CAROTID OCCLUSION
ITS DIAGNOSIS BY OPHTHALMODYNAMOMETRY DURING CAROTID COMPRESSION

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PARTIAL or complete occlusion of the carotid vessels in the neck is a common cause of stroke. Bull et al. (1960) found angiographic evidence of carotid occlusion in 14 (17·5%) of 80 consecutive admissions for stroke at Queen Square, and Barham-Carter (1960) reported an incidence of 20% in postmortem studies of cerebral infarction.

At present, clinical methods for the diagnosis of carotid occlusion are of limited value, while cerebral angiography carries an appreciable morbidity and mortality and is not justified as a routine procedure in all cases of stroke (Bull et al. 1960, Baker 1960). A simple and reliable bedside test for the presence of carotid occlusion would therefore be a valuable aid in diagnosis, or in the selection of patients for angiography.

Ophthalmodynamometry

The retinal artery pressure can be measured in conscious patients with an ophthalmoscope and ophthalmodynamometer. When an increasing force is applied to the outside of the eyeball, the retinal artery pulsates freely as soon as the applied pressure exceeds the retinal artery diastolic pressure, and ceases to pulsate when systolic pressure is exceeded. The procedure is simple, and in practised hands reliable, and is adequately described elsewhere (Thomas and Petrohelos 1953, Wood and Toole 1957).

Rubino (1911) first reported that carotid artery ligation lowered retinal artery pressure in a rabbit, and Baurman (1936) and Miletti (1946, 1950) have reported similar findings in man. Since then Kirby and Hollenhorst (1954), Zvien and Hollenhorst (1956), Heyman et al. (1957), Wood and Toole (1957), Hollenhorst (1958), and Smith et al. (1959) have amplified these results and report that carotid occlusion and ligation may cause a difference in retinal artery pressure on the two sides. Thomas and Petrohelos (1953) summarised their own and other workers' findings, reporting that in 249 control patients the difference between retinal artery pressure readings in the two eyes did not exceed 15%, whereas in carotid occlusion the difference often exceeded this figure. The whole subject is well reviewed by Wagener (1959), who gives further references.

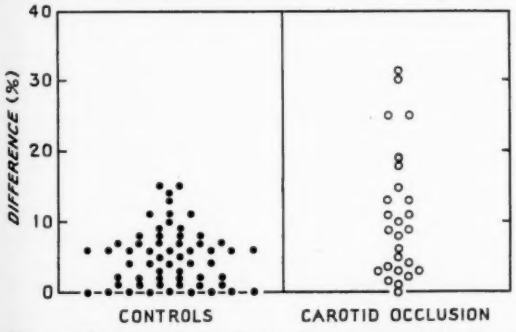

Fig. 1—Difference between retinal artery pressures in the two eyes in man.

Diastolic pressure differences in the retinal artery were studied by us in 26 patients with carotid occlusion, and 63 controls (fig. 1). The normal difference was up to 15%, but in our series only 6 cases (23%) of carotid occlusion showed differences greater than this.

Other workers have reported that systolic readings may improve on these results, but these have not been used systematically by us because: (1) they have a higher observer error, (2) repeated measurements cannot be taken in rapid succession, and (3) many of our patients were hypertensive and had systolic readings beyond the range of the apparatus.

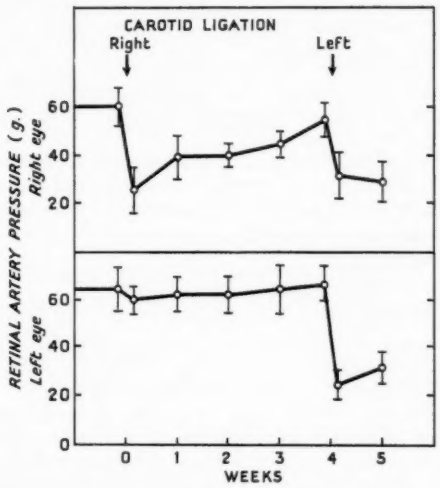

Fig. 2—Retinal artery pressures in 26 rabbits, after successive carotid ligation at four weeks' interval.

To analyse this problem further, investigations were made in rabbits.

Investigations in Rabbits

The rabbit has a circle of Willis very like that in man, with two internal carotids and a basilar system linked by anterior and posterior communicating channels (McDonald and Potter 1951).

Rabbits were anæsthetised with pentobarbitone (90 mg.) and ether; internal and external carotid arteries on one side were cut between ligatures. Retinal artery pressure readings were taken in duplicate in each eye before and after this procedure, and weekly thereafter. In the rabbit the systolic end-point proved more accurate than the diastolic and was used throughout.

In all rabbits, carotid ligation produced a fall in retinal artery pressure on the same side, with no significant change in the pressure in the contralateral retinal artery; but this pressure difference disappeared over the succeeding four weeks. Ligation of the carotid vessels on the other side, four weeks after the first operation, resulted in a fall in pressure in both eyes,

TABLE I—RETINAL ARTERY SYSTOLIC PRESSURE CHANGES ON COMMON CAROTID CLIPPING IN RABBITS (MEAN OF 26 RABBITS)

	Fall in pressure (%)	
	Right eye	Left eye
Normal rabbits:		
Clip right carotid	50	0
Clip left carotid	0	50
Rabbits with right carotid occlusion:		
Clip right carotid	0	0
Clip left carotid	40	64

Differences from normals: (1) no ipsilateral fall on clipping *right* carotid; (2) unusually large ipsilateral fall on clipping *left* carotid; (3) asymmetry of ipsilateral falls; and (4) crossover fall of retinal artery pressure in *right* eye when *left* carotid is clipped.

demonstrating that the main part of the collateral supply had come from the opposite carotid system (fig. 2).

Three-quarters of the rabbits, four weeks after the first carotid ligation, had differences in retinal artery pressure within normal limits, but they could be clearly distinguished from normals by a simple test. Retinal artery pressures were recorded in these rabbits before and after momentarily occluding each common carotid in turn with a bulldog clip, and the results are shown in table I.

Yet a third pattern was seen in rabbits with bilateral carotid ligation. They showed a retinal artery pressure abnormally low compared to their blood-pressure, with no fall on clipping either carotid.

We therefore thought it worth finding out whether these patterns were present in human carotid occlusion, substituting percutaneous compression of the common carotid for the bulldog clip.

Ophthalmodynamometry with Carotid Compression in Man

Baurman (1936) first reported the influence of carotid compression on retinal artery pressure in man. Miletti (1946, 1950) extended these observations to 30 normals and 5 patients with carotid occlusion, reporting that in the latter condition compression on the side of the lesion had no effect, but that compression of the patent carotid produced falls in both eyes. Since then there have been a number of reports of the effect of carotid compression in normals (Van Allen and Bodi 1958, Heyman et al. 1960, Tindall et al. 1960), but no observers have studied systematically the effects in patients with carotid occlusion. Wagener (1959) suggests that the probable reason for this omission was the fear of producing severe symptoms during compression of the common carotid for the two to three minutes suggested by Miletti.

Our observations in the rabbit showed that the retinal artery pressure remained fairly constant for many hours after carotid occlusion, and that the full effects were seen virtually instantaneously after the occlusion. We have accordingly used very short periods of compression in man.

Method

The subject lay supine with his eyes fixed on a spot overhead after cocaine and homatropine eyedrops (2%) had been instilled. The blood-pressure was recorded by sphygmomanometer, and immediately afterwards diastolic retinal artery pressure readings were taken in duplicate in each eye, to assess resting pressure differences. A second observer palpated the neck and practised carotid compression until satisfied that he could produce rapid and complete obliteration of the common carotid on each side in turn. Retinal artery pressure readings were then taken in one eye before, during, and immediately after carotid compression. Duplicate readings were taken for compression of each carotid in turn, and the whole procedure repeated on the opposite eye.

The ophthalmodynamometer used was Baillart's dial-type (illustrated by Heyman et al. 1957). The instrument is graduated in units of 5 g. but readings were taken to the nearest gramme. Readings in grammes with this instrument are approximately equivalent to retinal artery pressure in mm. Hg (Perry and Rose 1958). All readings were repeated until duplicates gave good agreement—commonly to within 4%.

Carotid compression was carried out as low in the neck as possible, and its completeness assessed either by the compressing thumb, or in difficult cases by palpation of the pulse above the point of compression. The duration of compression was normally three to ten seconds—i.e., the minimum period necessary to obtain a retinal artery pressure reading.

Subjects

Technically satisfactory tests were carried out in 63 controls and in 28 patients with carotid occlusion. Controls were chosen predominantly from a hypertensive clinic, and 24 of them had had a stroke. The age-distribution of controls and patients with carotid occlusion was similar. The diagnosis of carotid occlusion was based on: (1) unequivocal angiographic findings (20 cases); (2) operative findings (ligation for aneurysm 5, diagnostic exploration 1); and (3) complete absence of any carotid pulsation above the thyroid cartilage on one side (2). The possibility cannot be completely excluded that the controls may have included a case of undiagnosed carotid occlusion since angiography had not been performed on 10 of the patients with stroke.

Technical Difficulties

The commonest cause of failure to obtain satisfactory readings was inability of elderly disorientated patients to keep their eyes open and still (6 cases). Local ocular causes (cataract and retinal artery occlusion) caused failure in 3 cases, but even in their presence, results from one eye may be of value (case 18).

Compression of the common carotid too high in the neck produced bradycardia and falls in blood-pressure with resulting bilateral falls in retinal artery pressure, probably due to carotid sinus compression. This "sinus effect" could be readily detected by the retinal artery pressure reading taken immediately after release of compression. This should normally be the same as the precompression value, whereas if the blood-pressure has fallen, the reading does not return instantaneously to its precompression value, but creeps back over thirty to sixty seconds. Occasionally, in fat short-necked patients the sinus effect cannot be eliminated, however low in the neck the carotid is compressed. In these patients the readings accepted are those during and immediately after release of compression.

Complications

None of the controls, and only 3 out of 28 patients with carotid occlusion, showed any transient neurological symptoms. These disappeared immediately on release of compression. An elderly hypertensive patient noticed blurring of vision three days after testing; this was due to a retinal vein thrombosis, but may have been fortuitous.

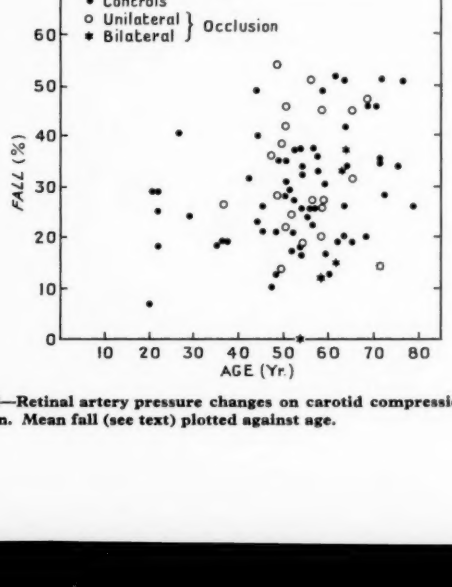

Fig. 3—Retinal artery pressure changes on carotid compression in man. Mean fall (see text) plotted against age.

Results

All retinal artery diastolic pressure readings are expressed in grammes of ophthalmodynamometer pressure, and falls on compression are percentages of the starting level.

The following terms will be used:

1. *Ipsilateral fall.*—Percentage reduction in retinal artery pressure in one eye during compression of carotid on the same side.
2. *Mean fall.*—Mean of the two ipsilateral falls in one subject.
3. *Asymmetry.*—Difference between the two ipsilateral falls.
4. *Crossover fall.*—Fall in retinal artery pressure in one eye during compression of the opposite carotid.

Controls

All subjects showed some ipsilateral fall in each eye, ranging from 5% to 62%. The mean fall ranged from 7% to 52% and bore no obvious relation to age (fig. 3) or to sex. There was commonly some asymmetry, with a maximum of 22%. No crossover fall occurred in any subject (provided that the " sinus effect " was excluded).

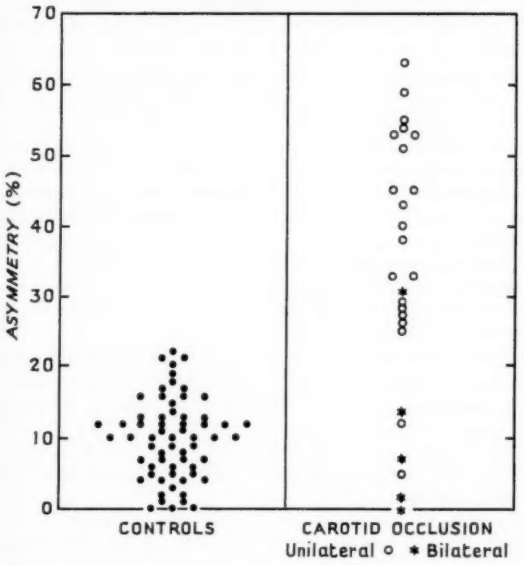

Fig. 4—Retinal artery pressure changes on carotid compression in man.
Asymmetry = the difference between the two ipsilateral falls.

Patients with Unilateral Carotid Occlusion (23)

The mean fall ranged from 14 to 54% (fig. 3). Five features were seen, which were not found in any controls: (1) asymmetry was 25% or more (19 patients) (fig. 4); (2) crossover fall (on compression of the patent carotid) ranged from 11 to 49% (15); (3) the ipsilateral fall on the side of occlusion was nil (9); (4) the ipsilateral fall on the patent side was 65% or more (6); and (5) the resting retinal artery pressure difference was more than 15% (6).

The distribution of these features in the 23 patients is shown in table II. The findings in common carotid occlusion are more grossly abnormal and exactly fit the patterns seen in rabbits. Among less severe degrees of carotid occlusion (17 cases), at least one feature was seen in every patient, except case 19. 2 patients with partial occlusion are included, and these show the same features as complete occlusion.

The most reliable single diagnostic criterion was asymmetry. Only cases 8 and 11 failed to show this, but case 8 had a 19% difference in resting pressures, and case 11 had a 41% crossover fall. 2 patients were seen in whom readings could be taken from one eye only; 1 of these had an ipsilateral fall of 72% (higher than any control subject), and the other 56% (higher than most control subjects). Of the 23 patients, 22 are therefore clearly abnormal, and the remaining patient probably would have been, had readings been possible in both eyes.

TABLE II—FEATURES OF RETINAL ARTERY PRESSURE IN CASES OF UNILATERAL CAROTID OCCLUSION IN MAN

Diagnosis	Case	On carotid compression				Difference in resting R.A.P. 15%
		Asymmetry 25%	Crossover fall	Lesser ipsilateral fall = nil	Greater ipsilateral fall 65%	
Common carotid occlusion	1	+	+	+	..	+
	2	+	+	+	..	+
	3	+	+	+	..	+
	4	+	+	+	..	..
	5	+	—†	+	..	..
	6	+	+	+	..	+
Incidence (%)		100	100	100	Nil	67
Internal carotid occlusion and stenosis	7	+	..	..	+	..
	8	..	+	..	..	..
	9	+	..	..	+	..
	10	+	+	..	..	..
	11	..	..	..	..	+
	12	+	+	+	..	..
	13	+	+	..	+	..
	14	+	+	+	..	..
	15	+	..	..	+	+
	16	+	+	..	..	..
	17	+	..	+	..	..
	18	No reading—cataract			+	No reading
	19	"	"	"	..	" "
	20	+	+	..	+	..
	21	+	+	..	..	..
	22*	+	+	..	..	..
	23*	+	+	..	..	..
Incidence (%)		87	67	20	25	13
Total incidence (%)		90	75	43	26	29

* Stenosis. † Anterior communicating artery ligated.
R.A.P. = retinal artery pressure.

Patients with Bilateral Carotid Occlusion (5)

No patient had a significant difference in resting pressures. In 2 of the 5 the occlusion was not bilaterally symmetrical, and these 2 had results resembling unilateral occlusion—asymmetry in case 28 and a crossover fall in case 26. Of the remaining 3, 2 showed the pattern seen in rabbits with bilateral occlusions—i.e., retinal artery pressures unusually low for the diastolic blood-pressure (fig. 5), and unusually small mean falls of 12% and 0%.

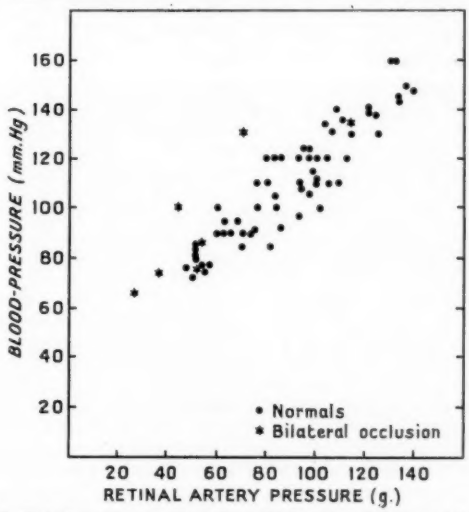

Fig. 5—Relation between diastolic retinal artery pressure and diastolic blood-pressure in 61 normals and 7 patients with bilateral carotid occlusion.

TABLE III—FEATURES OF RETINAL ARTERY PRESSURE IN CASES OF BILATERAL CAROTID OCCLUSION IN MAN

Case	On carotid compression			Retinal artery pressure abnormally low compared with blood-pressure	Diagnosis
	Asymmetry	Crossover fall	Lesser ipsilateral fall = nil		
24	..	..	..	+	Bilateral internal carotid occlusion.
25	..	..	..	..	Known right internal stenosis; probable left internal stenosis.
26	..	+	..	..	Right internal occlusion; left external occlusion.
27	..	..	(both sides) +	.. +	Bilateral severe stenosis.
28	+	..	+	?+	Right common carotid occlusion; left internal carotid occlusion.

4 out of 5 patients are thus clearly distinct from the controls (table III).

The remaining patient, case 25, was indistinguishable from normal in every respect—i.e., mean fall 37%, asymmetry 2%, crossover fall 0%.

Postoperative Changes

3 patients were studied after attempted disobliteration of their carotids.

In case 7, operation was unsuccessful and the patient developed a complete hemiplegia and aphasia, with absence of any pulsation in internal or external or carotid arteries. After operation the ophthalmodynamometric results were now those of common carotid occlusion—case 1.

In case 23, operation was successful and after operation there was only 15% asymmetry, with no crossover fall.

In case 25, the right side only was explored and disobliteration successfully performed. After operation the findings were characteristic of a residual left-sided occlusion, with 25% asymmetry and a crossover fall of 5%.

Interpretation

Interpretation of these results depends upon the assumption that the ophthalmodynamometer readings are approximately proportional to perfusion pressure available in the internal carotid artery at the origin of its ophthalmic branch. If we accept this as a working hypothesis, the findings are best explained thus:

1. Ipsilateral fall represents the contribution of the internal carotid to the ophthalmic artery pressure plus any collateral supply from the external carotid. There is, therefore, no ipsilateral fall in any case of common carotid occlusion, but an ipsilateral fall is normal in internal carotid occlusion, even when the occlusion is complete.

2. Crossover fall is a measure of the collateral supply via the anterior communicating artery, and is present in every case of common carotid occlusion, except when the anterior communicating artery has become occluded (case 5).

3. Asymmetry (the difference between the two ipsilateral falls) is a feature dependent on two factors, which normally occur together—asymmetry of collaterals and asymmetry of carotid flow. The basic factor tested by measuring asymmetry is the ability of the collateral circulation to maintain the ophthalmic artery pressure in the absence of carotid flow from the same side. The commonest cause of asymmetry is reduced internal carotid flow on one side, which is the stimulus to the opening up of a collateral circulation. Asymmetry, however, is found immediately after acute obstruction (by compression) of a normal carotid. The factor causing asymmetry here is clearly not anatomical asymmetry of collaterals, but functional asymmetry of flow in the carotids. It seems reasonable, therefore, to regard asymmetry as a rough measure of the difference between total carotid flow on the two sides.

A number of suggestions can now be made for the adaptations in the circle of Willis which follow carotid occlusion:

1. After sudden occlusion of the internal carotid, the pressure is lowered in the quadrant of the circle supplied by that carotid.

2. Perfusion pressure is restored towards normal by the opening up of collaterals.

3. The main collaterals concerned are the external carotid and the two communicating arteries, but these supply collateral flow in proportions which differ from subject to subject. In most instances a significant supply comes via the external carotid, which may supply half the total collateral flow (case 8).

4. During gradual progressive carotid stenosis the collateral flow develops in step with stenosis, and the pressure above the stenosis is maintained at nearly normal levels.

Discussion

Ophthalmodynamometry with carotid compression is a simple procedure, but to decide whether it has any clinical application its advantages and disadvantages must be compared with those of carotid angiography.

The diagnostic accuracy of both is over 90%.

Ophthalmodynamometry is much simpler and quicker than angiography. It causes much less morbidity and less discomfort to the patient. It requires less apparatus and preparation, but it does need more cooperation from the patient.

Carotid angiography shows the site and degree of an occlusion, but ophthalmodynamometry will not demonstrate the site, or whether internal carotid occlusion is partial or complete.

Each procedure has its limitations in diagnosis, and either may succeed where the other has failed. Ophthalmodynamometry will fail to detect certain types of bilateral stenosis; and carotid puncture will fail to detect stenosis at the origin of the common carotid or innominate stenosis, and is often less accurate in the diagnosis of stenosis in the carotid siphon.

Ophthalmodynamometry shows only the state of the carotid vessels, while angiography may reveal other intracranial causes of stroke.

Ophthalmodynamometry merits trial:

1. As a screening test for the presence of carotid occlusion in the routine investigation of all strokes. Angiography could then be reserved to demonstrate the site and degree of occlusion.

2. As the only diagnostic procedure in the early stage of an acute stroke, when emergency carotid surgery may reverse advancing cerebral ischæmia, provided that no time is wasted.

3. In epidemiological and follow-up studies on the incidence and course of carotid stenosis.

If both angiography and ophthalmodynamometry are to be performed, ophthalmodynamometry should be done first, because the carotids remain tender to compression for several days after puncture.

Summary

In only 6 out of 28 cases of carotid occlusion in man was there a significant difference between the retinal artery pressures in the two eyes.

Investigations in rabbits suggested a modified test for the presence of carotid occlusion in man, using ophthalmodynamometry with carotid compression.

25 out of 28 cases (93%) of carotid occlusion were clearly distinguishable from normal by this test.

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TRANSPLANTATION OF A KIDNEY FROM AN IDENTICAL TWIN

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SUCCESSFUL transplantation of a kidney from an identical twin donor has been reported by Murray and his colleagues at the Peter Bent Brigham Hospital, Boston (Merrill et al. 1956, Murray et al. 1958), and later by Hume (1958) and Dossetor et al. (1960). Our report is concerned with another transplantation of this kind, which was performed at the Edinburgh Royal Infirmary in October, 1960. The case has some unusual features, and is, we believe, the first successful transplantation of the human kidney to be performed in Britain.

Patient and Donor

The Patient

A 49-year-old steel warehouseman, admitted to hospital on Sept. 15, 1960, gave a history of a dull aching pain in the interscapular region for 2 months. The pain, which was brought on by exertion, radiated to the retrosternal area, and had been more frequent during the few weeks before his admission. During this time he had also noticed that his face had become slightly œdematous, his ankles had been swollen in the evenings, and he had become breathless on exertion. He had been unable to work for 10 days because of extreme tiredness. For some years he had passed urine once during the night, but apart from this he had no symptoms referable to the urinary tract, and no previous history of renal disease.

He was pale and slightly confused, with a coarse tremor of the arms and hands. The jugular venous pressure was not raised, but there was a trace of ankle œdema. The blood-pressure was 178/102 mm. Hg. The heart was not enlarged on clinical evidence; the sounds were of good quality; and a grade-I systolic murmur was audible at the base. No pericardial friction was detected. The retinæ showed grade-III changes with markedly increased light reflex, A-V nipping, and a few small hæmorrhages and exudates in both fields (fig. 1*a*). Neither kidney was palpable, and the prostate was not enlarged. A chest radiograph showed left ventricular hypertrophy, the transverse diameter of the heart being 150/300 mm. The electrocardiogram (E.C.G.) was within normal limits.

On admission the blood-urea-nitrogen was 108 mg. per 100 ml. and 2 weeks later it had risen to 141 mg. Metabolic acidosis was considerable (serum-bicarbonate 10 mEq. per litre), and the serum-potassium was slightly increased (5·5 mEq. per litre). The patient was treated by intravenous infusion of dextrose and 1/6 *M* lactate; later he had a diet containing 40 g. of protein per day, and sodium bicarbonate by mouth. On this regimen his general condition improved, the blood-urea-nitrogen fell to 48–60 mg. per 100 ml., and the metabolic acidosis lessened.

The 24-hour volume of urine ranged from 1·0 to 2·7 litres, the osmolality of an early morning specimen being 316 mOsmol. per kg. The urine contained protein 1·0–1·6 g. per 24 hours; microscopically a centrifuged specimen showed 25–30 red blood-cells (R.B.C.) and 1-2 white cells (W.B.C.) per high-power field. Occasional granular casts were present. Enterococci were cultured from the urine once.

The 24-hour creatinine-clearance, determined on five occasions, was 10–13 ml. per min. The values were also low for the clearance of inulin (6 ml. per min.) and *p*-aminohippuric acid (24 ml. per min.). The effective renal blood-flow, measured by *p*-aminohippuric acid, was 36 ml. per min., the filtration fraction being 25%. These figures are the mean of the values during five separate clearance periods, each of 15–20 minutes.

Intravenous pyelography (I.V.P.) did not reveal any trace of a shadow on either side. On cystoscopy there was a normal ureteric orifice on the left, but none on the right; apart from this the bladder appeared normal.

On admission the hæmoglobin (Hb) was 51%; the hæmatocrit, 24%; R.B.C., 3·34 million per c.mm; mean corpuscular volume (M.C.V.), 72 c.μ; mean corpuscular Hb concentration (M.C.H.C.), 31%; W.B.C., 8000 per c.mm; platelets, 200,000 per c.mm; erythrocyte-sedimentation rate (E.S.R.), 40 mm. in the 1st hour (Westergren). 3 pints of whole blood were given before operation, bringing the Hb up to 72%.

We considered that the gross impairment of renal function was probably the result of chronic pyelonephritis, although chronic glomerulonephritis could not be excluded. In either event the prognosis with conventional

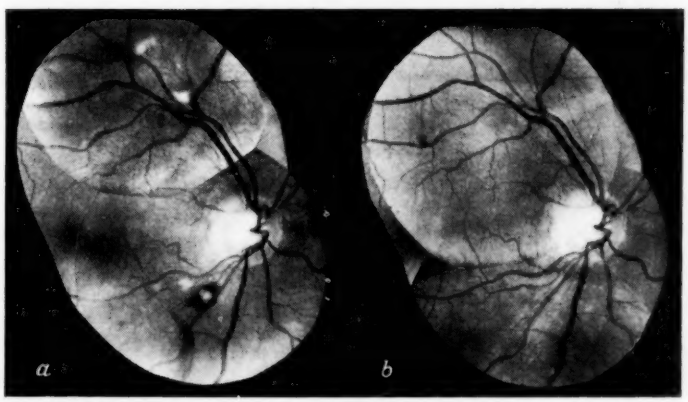

Fig. 1—Retinal photographs: (*a*) before operation, and (*b*) 10 weeks after operation.
The retinopathy is much improved in (*b*), with disappearance of hæmorrhages and exudates.

treatment was poor. With the possibility of renal transplantation in mind the patient was asked if he happened to have a twin. He replied that he had a twin brother.

The Donor

The twin was in good health, and examination revealed no abnormality. The urine contained no protein or cells, and was sterile on culture. The blood-urea-nitrogen was 15 mg. per 100 ml. and the creatinine-clearance was 88 ml. per min. The Hb was 100%, and the E.S.R. 2 mm. in the 1st hour. A plain radiograph showed that both kidneys were of normal size, and an I.V.P. showed good excretion of dye on both sides 5 minutes after injection. Cystoscopy revealed no abnormality.

Evidence that the Twins were Identical

The twins had often been mistaken for each other; and, allowing for the fact that one was seriously ill, their general appearance, including eye colour, shape of the hair line, and shape of the ears, was very similar. Indeed, on this evidence alone, Dr. D. Michie thought they were probably identical.

Blood-grouping (by Dr. K. L. G. Goldsmith at the Blood Group Reference Laboratory, Lister Institute, London) revealed no difference in red-cell antigens, the formula in each case being as follows: A1B; ccDEe; MN; S+; P1−; Lu^a-; K−; Le^a-; Le^b-; Fy^a-. The relative probability of twins of like sex showing these similarities being dizygotic, calculated from the tables of Maynard-Smith and Penrose (1955), is 0·023.

Finger and palm prints were examined for us by Prof. L. S. Penrose at University College, London. He found great similarity, with some degree of mirror-image pattern; and on the basis of two metrical tests (namely, the difference in total finger-ridge counts, and the difference in the sum of left and right maximal *atd* palmar angles [Penrose 1949, Maynard-Smith and Penrose 1955]) he calculated the relative probability of the pair being dizygotic as 0·18.

The serum-proteins were investigated by Dr. Bernard Cohen at the University of Glasgow. He reported that both twins possessed haptoglobin type 2-1, and that the relative probability of a pair of twins who both possess this phenotype being dizygotic (when the parents' genotypes are unknown) is 0·62. The final relative probability that these twins were dizygotic is thus, on the tests enumerated, $0{\cdot}023 \times 0{\cdot}18 \times 0{\cdot}62 = 0{\cdot}0026$.

Finally, full-thickness skin grafts of 1 × 1 cm. were exchanged between the twins under local anæsthesia. These took satisfactorily, and have remained healthy ever since; in particular they have never shown any trace of scabbing, and have retained their original size (fig. 2).

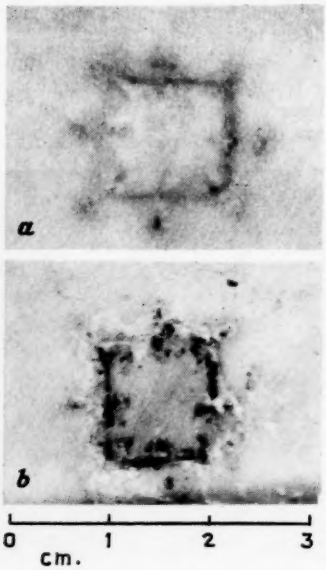

Fig. 2—(*a*) Skin graft from patient to healthy twin, after 4 weeks; (*b*) skin graft from twin to patient, after 6 weeks.

When it appeared virtually certain that the twins were monozygous the situation was explained to the healthy one, who volunteered to donate a kidney. His formal consent was expressed as follows:

"Knowing that my twin brother, Mr. L. A., is suffering from a serious and incurable disease of his kidneys, I have volunteered to give one of my own two healthy kidneys to be used as a graft to my brother, and I agree to the grafting operation being carried out by Prof. M. F. A. W. and Mr. J. A. R. in the Edinburgh Royal Infirmary. The possible risks of the procedure have been explained to me."

Operation

Renal transplantation was performed on Oct. 30. One operating-team was responsible for the donor; another, working in an adjacent theatre, for the patient.

Operation on the Donor (J. A. R.)

After the donor had been anæsthetised retrograde aortography was attempted by Dr. Eric Samuel, with the object of finding if there was any abnormality of the renal arteries, in particular a double artery on one or both sides. Unfortunately, however, the catheter could not be advanced into the aorta, apparently owing to tortuosity of the iliac arteries, and it was not considered justifiable to perform translumbar aortography at this stage.

The left kidney was approached through the bed of the 12th rib, by the technique of Sames (1950). An excellent exposure was obtained, and the kidney was easily handled without forcible retraction or traction on the pedicle. After opening the perinephric fascia and entering Gerota's box, the kidney was gently freed from some adhesions, and dissection of the renal pedicle was begun. Two main renal arteries of equal calibre were demonstrated, and followed medially through somewhat fibrosed fatty tissue towards the aorta. It was hoped they would meet to form a single channel, but they remained separate throughout their course, and a slender filament from the left diaphragmatic crus passed between the two arteries at their junction with the aorta. The left renal vein was a single channel, though there were two separate left spermatic veins opening into it.

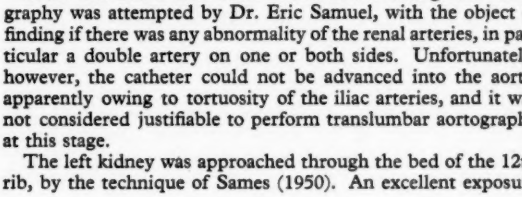

Fig. 3—Method to deal with the double renal artery.
A = longitudinal incision 1 cm. long in each vessel; B = ends opened out; C = ends of vessels sutured together to form a single channel.

The left ureter was divided at the brim of the pelvis. Heparin (1000 units) was injected (as advised by Küss et al. 1960) into each renal artery, and these were then clamped and divided. The renal vein was divided immediately afterwards. The kidney was then removed, placed in a basin where it was surrounded with swabs soaked in ice-cold saline, and taken through to the recipient. The wound was closed in the normal way.

Operation on the Patient (M. F. A. W.)

A long oblique incision was made parallel to Poupart's ligament and about 5 cm. above it. The muscles of the abdominal wall were divided to expose the peritoneum, and the right rectus muscle was cut across near its lower end. The peritoneum was stripped to expose extraperitoneally the common and external iliac arteries with the corresponding veins. The absence of ureter and kidney on the right was confirmed.

At this stage it was learned that the kidney graft had two separate renal arteries. It was decided to anastomose one of these to the anterior branch of the internal iliac artery, and the other to its posterior branch, but this plan had to be abandoned when the recipient was found to have an atheromatous plaque just proximal to the point of bifurcation of the internal iliac artery. The two arteries of the donor kidney were therefore sutured together to form a single channel (fig. 3), and this composite vessel was anastomosed end-to-side to the external iliac artery near its origin. Whilst this was being done sterile ice-cold saline was dripped continuously on to the kidney,

and seemed to cool it effectively. The single vein of the transplant was anastomosed end-to-side to the external iliac vein. For the arterial anastomosis two stay sutures were inserted, and these were united in front and behind by a simple over-and-over stitch. For the venous anastomosis four everting stay sutures were inserted and joined with a continuous everting stitch.

The kidney was deprived of its circulation for 85 minutes. When the clamps were released, it became pink almost instantly. The blood-flow was obviously well established, but a thrill could be felt at the site of the arterial anastomosis. The ureter showed vigorous peristalsis almost immediately the arterial clamps were released, but secretion of urine was not seen.

The bladder was opened and an oblique tunnel was made through its wall from within outwards with artery forceps. The ureter was drawn into the bladder through this opening, and transected obliquely at about the junction of its upper and middle thirds. Mucosa-to-mucosa anastomosis was then made with 3/0 plain catgut. A piece of soft plastic tubing (polyvinyl chloride, 3 mm. outside diameter) was passed into the ureter, and attached to the mucosa of the bladder with a fine catgut stitch. This tube was brought out through the anterior wall of the bladder and the abdominal wall. A no. 18 Foley catheter was passed up the urethra to the bladder, which was then closed. The large abdominal wound was closed in layers after a Penrose drain had been inserted down to the site of the graft, using continuous chromic catgut for the muscles, and silk for the skin.

The Donor

Course after Operation

The donor made an uneventful recovery and was discharged to a convalescent hospital after 2 weeks. At this time the blood-urea-nitrogen was 20 mg. per 100 ml., the serum-creatinine 1·86 mg. per 100 ml., and the creatinine-clearance 69 ml. per min. He returned to work 3 weeks later.

The Patient

Dextrose solution was given intravenously for 48 hours, after which the patient had all his fluids and electrolytes orally. In a few days he was able to take a light diet, the protein content of which was gradually increased. A tendency to acidosis was corrected by giving sodium bicarbonate 2–6 g. daily by mouth for 4 weeks. In view of the atherosclerosis, and the technical difficulty of the arterial anastomosis, heparin (2000 units every 6 hours) was given intravenously for 48 hours. Phenindione was started by mouth 24 hours after the operation, and it has been continued since, the dosage being adjusted according to the prothrombin-time and thrombotest. At present it averages 75 mg. per day, and the prothrombin-time is $1^1/_2$ to 2 times the control.

The postoperative course was remarkably smooth except for a transient right hemiparesis 14 days after operation (2 days after the patient was first allowed out of bed), which cleared completely in a few days.

During the first 24 hours after operation 78 ml. of urine was collected from the transplant. During the next 48 hours the volume was only 44 ml., but the collecting tube was found to be kinked, and in the 24 hours after this obstruction was relieved 1650 ml. was collected. Next day the output was 2055 ml., and by the 6th day it had risen to 2200 ml. At this time the tube was taken from the ureter, and thereafter only mixed urine was collected. The bladder catheter was removed after 12 days. Until then no antibiotics were given, but as urine cultures yielded a fairly profuse growth of *Bacillus proteus* the patient was given chloramphenicol 14 g. in the course of a week, followed by streptomycin 10 g. over 5 days, after which the urine became sterile.

The effect of the transplantation on the patient's renal function is summarised in fig. 4. By the 24th postoperative day the blood-urea-nitrogen had fallen to normal limits, although the patient's diet then contained 60 g. of protein daily, and the creatinine-clearance had risen to about 60 ml. per min. The osmolality of the 24-hour urine specimens ranged from 260 to 320 mOsmol. per kg.; and an attempt on the 12th day to induce water diuresis caused a reduction in the serum-sodium level to 126 mEq. per litre. When pitressin tannate (20 pressor units) was injected intramuscularly, and water was withheld for 14 hours, the urine osmolality rose to 640 mOsmol. per kg.

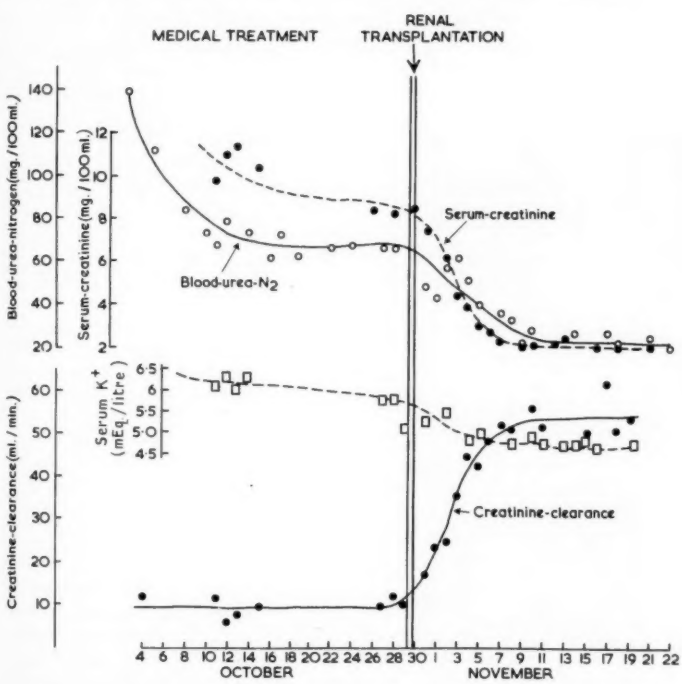

Fig. 4—Effect of medical treatment and of renal transplantation on the blood-urea-nitrogen, serum-potassium, and creatinine-clearance.

The patient was discharged to a convalescent hospital 7 weeks after operation, without any dietetic restriction. He was readmitted to the Edinburgh Royal Infirmary 10 days later for reassessment.

He had gained weight and looked very well, and he was no longer dyspnœic on exertion. The blood-pressure was 154/88 mm. Hg. Chest radiographs showed that the left ventricle was smaller, and the transverse diameter of the heart had fallen to 125/300 mm. The E.C.G. showed no change. The retinopathy was much improved (fig. 1*b*); the A-V nipping had largely disappeared, and only one small hæmorrhage was visible, though the retinal arteries still showed an increase in the light reflex. The blood-urea-nitrogen was 19 mg. per 100 ml., and the serum-electrolytes were within normal limits.

Further tests were performed 11 weeks after operation. The Hb was 79%; hæmatocrit 40%; M.C.V. 90 c.μ; M.C.H.C. 31%; W.B.C. 6000 per c.mm. The glomerular filtration-rate, as measured by the clearance of inulin, had risen to 56 ml. per min. The clearance of *p*-aminohippuric acid and the effective renal blood-flow had also increased to 265 ml. per min. and 434 ml. per min. respectively. The urine contained protein 1·5 g. per 24 hours, and on culture it yielded a scanty growth of enterococci and *B. proteus morgagni*. Cystoscopy revealed no evidence of bladder infection. The ureterovesical anastomosis looked like a small sentinel pile.

A retrograde pyelogram on the left showed that the renal pelvis and calyces were well defined and not dilated, but the kidney itself was very contracted, measuring only 8 cm. in its longitudinal axis. It seemed inadvisable to catheterise the ureter of the transplant at this stage. I.V.P. confirmed that the transplant was functioning well; the renal pelvis was clearly seen in the 5-minute film, and the ureter and bladder in later films. There was no trace of hydronephrosis.

The ability of the transplanted kidney to conserve sodium was excellent as tested by giving the patient a diet containing only 22 mEq. of sodium per day. The urinary excretion, which at the start of the test was 227·0 mEq. per 24 hours, fell on successive days to 41·0, 15·5, 15·1, and 8·6 mEq. per 24 hours. The ability to concentrate urine was also tested; after 16 hours deprivation of food and water, and the administration of pitressin tannate (20 pressor units) in oil, the urine concentration rose to 600 mOsmol. per kg., equivalent to a U/P osmolal ratio of 2·0.

The capacity to excrete hydrogen ion was tested by the procedure of Wrong and Davies (1959), in which the urinary excretion of titratable acid, the urinary ammonium, and the urine pH are measured hourly for 8 hours after giving ammonium chloride by mouth in a dose of 0·1 g. per kg. bodyweight. In our patient the pH of the urine fell to 4·90 at the 2nd hour and remained low for the remainder of the test, the lowest value being 4·82. The excretion of titratable acid rose to a maximum of 34 μEq. per min., and of ammonium ion to 54 μEq. per min. These values fall within the range of normal.

The patient returned to light work on Feb. 13, 1961—i.e., 106 days after the transplantation. A further I.V.P. (fig. 5) a month later confirmed that the transplanted kidney was functioning well.

Discussion

Medical treatment can do much to overcome the metabolic consequences of renal failure, and the preoperative improvement in our patient, including the remarkable fall in blood-urea-nitrogen, illustrates this fact well. Hæmodialysis, though not used in this case, has greatly increased the therapeutic possibilities, and the recently developed 'Teflon' prostheses, designed to remain connected to an artery and vein for weeks or months (Scribner et al. 1960), may facilitate the treatment of chronic cases by repeated dialysis.

The fact remains, however, that the only way of supplying new functioning nephrons is by transplantation. Until a clinically acceptable general solution to the immunological homograft problem has been found (for review, see Woodruff 1960), the indications for renal transplantation will remain narrow. While the patient may have little to lose and much to gain, it is clearly not justifiable to ask a donor to part with a healthy kidney which has only a small chance of functioning successfully as a transplant, until every other possible form of treatment has been tried; and even then only after most careful consideration of all the circumstances. The position would be different if cadaver kidneys could be available soon enough after death, but this too presents very great difficulty.

In the special case of a patient with an identical twin, there is no immunological barrier to successful transplantation. There are still problems because the disorder which the patient has may be actually present, or likely to develop, in the twin. But there must be many cases, like the present one, in which this is not so, and in our view renal transplantation would be performed more often if patients with renal failure were asked routinely if they had a twin.

The methods used to distinguish monozygotic from dizygotic twins have been discussed by Maynard-Smith and Penrose (1955) and are illustrated in this case. Interchange of skin grafts was first used deliberately for this purpose by McIndoe and Franceschetti (1950). As a preliminary to renal transplantation, skin grafting is harmless if the twins are in fact monozygotic; if they are dizygotic, however, the patient will become immunised against the tissues of the donor (and, incidentally, vice versa), and the immunological barrier to kidney transplantation will be even greater than before. In our view, therefore, preliminary skin grafting should be avoided unless, as here, it has been decided not to proceed unless the twins are monozygotic.

The morphology of the vessels of the donor kidney is clearly very important in relation to transplantation. Variations have been encountered previously by Murray et al. (1958), who reported that 3 of their donors' kidneys possessed either two or three renal arteries, and also by Dossetor et al. (1960), who found a double renal vein. Some idea of the frequency of these anomalies is desirable. Recent work on the renal circulation has been concerned mainly with the intrarenal vascular pattern, but information is to be found in older writings:

Quain (1892) stated that abnormalities of the renal arterial supply occur in about 25% of subjects, the commonest being a second artery. About 3% of subjects have three arteries, and four, five, or even six separate arteries are found occasionally.

Adachi (1928), in his extensive study of the arteries of the Japanese, found multiple renal arteries in 349 of 1500 subjects (23·3%), and he also described other abnormalities, such as variations in calibre, in site of origin, and in manner of origin.

The practical lesson is that aortography should be performed in possible kidney donors before contemplating transplantation. Our decision to delay aortography until the day of operation was taken to reduce the inconvenience to the donor, but in retrospect it was mistaken.

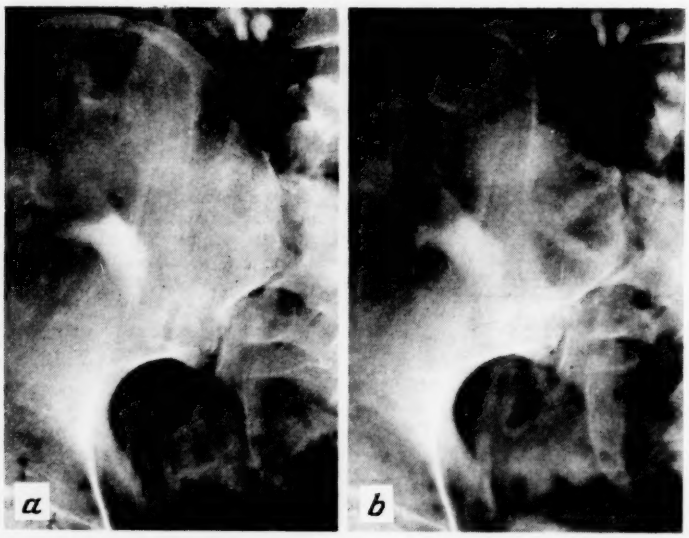

Fig. 5—I.V.P. 19 weeks after renal transplantation to the right iliac fossa: (*a*) 3-minute film, and (*b*) 12-minute film.

The transplant shows good function, and there is no dilatation of the renal pelvis or ureter.

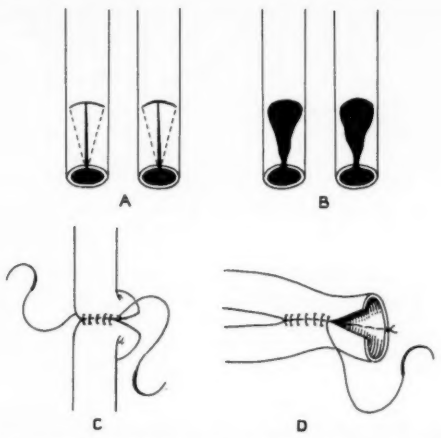

Fig. 6—Proposed method for dealing with a double renal artery.
In A and B each vessel is incised longitudinally, and two triangles of tissue are removed; in C and D the vessel ends are united by a continuous suture to form a single channel. (Compare fig. 3.)

The extraperitoneal approach to the recipient site proved entirely satisfactory, and it should, in our view, remain the standard procedure.

The method devised at the time for dealing with the double renal artery has worked quite well, but on reflection we think the modified technique illustrated in fig. 6 might be better. Whatever method is used the period of kidney ischæmia will inevitably be longer than when there is a single renal artery. It has been shown experimentally by Mitchell and Woodruff (1957), and confirmed by Birkeland et al. (1959), that the time for which the kidney will tolerate ischæmia can be increased significantly by keeping it cool; and it seems likely that the cooling employed in our case contributed to the rapid functional recovery.

The technique of dealing with the ureter was very satisfactory. We attach considerable importance to the fact that only the upper third of the ureter was retained with the transplant. In the first place this greatly reduces the risk of ischæmic necrosis. Secondly, there is evidence (Murnaghan 1960) that anastomosis made at a lower level (i.e., in the parts of the ureter derived from the embryological middle and lower spindles) may initiate reversed ureteric peristalsis, and lead to hydronephrosis; whereas anastomosis in the upper third should be free from these complications.

In the postoperative management there are three matters which call for comment. Firstly the policy of withholding antibiotics until after the urethral catheter was removed, and then giving large doses to which the organisms cultured from the urine were sensitive, was so successful that we should do the same again in similar circumstances. But it does not follow that the same policy should be adopted in patients given total body irradiation or cytotoxic agents before transplantation from a donor other than an identical twin, and our opinions are divided about what to do in such cases.

Secondly, the postoperative administration of anticoagulants certainly did no harm in this patient, and it was probably beneficial. We propose to continue phenindione therapy indefinitely.

Finally there remains the question of whether or not to remove the patient's own remaining kidney. So far we have not done so on the following grounds: (1) the dose of anticoagulants would probably have to be reduced temporarily if nephrectomy were done, and this might precipitate thrombosis in the arteries to the transplant; (2) the patient's own kidney, though poor indeed, is not entirely devoid of function, and might enable him to be kept alive for months—perhaps even years—by repeated dialysis if the vessels to the transplant did thrombose; and (3) so long as the blood-pressure remains reasonably low, and the urine from the patient's own kidney remains sterile, nephrectomy would only be indicated for chronic glomerulonephritis, and we think that chronic pyelonephritis is the more likely diagnosis.

Summary

This paper reports a successful renal transplantation from a male identical twin donor to his brother, who had irreversible renal disease with uræmia.

On the basis of blood-grouping, finger and palm prints, and haptoglobin analysis, the probability that the twins were dizygotic was estimated to be as low as 0·0026. Full-thickness skin grafts exchanged between the twins took satisfactorily and have remained healthy until now—a period of 8 months.

At operation the donor's kidney was found to have two main renal arteries which arose separately from the aorta. These arteries were sutured together to form a single channel, and the composite vessel was anastomosed end-to-side to the recipient's external iliac artery. The renal vein was anastomosed end-to-side to the recipient's external iliac vein, and the ureter to the bladder.

The donor made an uneventful recovery. Before operation the recipient's creatinine and inulin clearances were 12 and 6 ml. per min. respectively, and the effective renal blood-flow was 36 ml. per min. Renal function improved immediately after operation; 11 weeks later the creatinine and inulin clearances had risen to 60 and 56 ml. per min. respectively, and the effective renal blood-flow was 434 ml. per min. There was striking clinical improvement, with marked regression of the retinopathy.

Our great indebtedness to Prof. L. S. Penrose, Dr. Bernard Cohen, and Dr. K. L. G. Goldsmith is acknowledged in the text. We are grateful also to many colleagues in Edinburgh, including Dr. D. Michie, who advised us on the diagnosis of identical twins; Dr. R. A. Cumming, who performed the initial blood-grouping; Dr. A. Doig, who made the inulin and *p*-aminohippuric acid determinations; Dr. J. McC. Murdoch, who advised on measures to control infection; Dr. Eric Samuel our radiologist; Dr. J. D. Robertson and Dr. A. H. B. Masson, our anæsthetists; and Prof. George Scott, who made the retinal photographs.

M. F. A. W. and J. A. R. would like also to thank Mr. David Band, their urological colleague, who not only showed great interest in the case but graciously assisted at the operation.

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PREVALENCE OF DIABETES IN WOMEN THIRTEEN YEARS AFTER BEARING A BIG BABY

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THOUGH many diabetic women recall giving birth to one or more abnormally big babies (Allen 1939, Miller 1945, Kriss and Futcher 1948, Moss and Mulholland 1950), it is not known how often women who have had a big baby subsequently develop diabetes. The long interval which may elapse between the birth of a heavy child and the development of diabetes (Jackson 1952), together with the difficulty of collecting an otherwise unselected group of such women, has in the past been an understandable deterrent to getting this information.

During 1947 McKeown and Gibson (1951) collected records of the birthweight, name, and address of every baby born in Birmingham. The present study concerns the prevalence of diabetes, thirteen years later, in a sample of the mothers whose babies had been unusually large.

Method

21,940 live children were born in Birmingham in 1947; this figure includes births at home, in hospitals, and in nursing-homes. 458 (2·1%) weighed over 10 lb. at birth, and of these 134 (0·6%) weighed over $10^1/_2$ lb. (McKeown and Gibson 1951). 98 of the children who weighed over $10^1/_2$ lb. had previously been interviewed in another connection (Lowe and Gibson 1953). The mothers of these—a random sample of the total—provided the starting point for our investigation. 71 of the women could be traced and 61 (86%) cooperated in the study:

TABLE I—AGE DISTRIBUTION OF NORMAL AND DIABETIC GROUPS

Group	Age					
	30–	35–	40–	45–	50–	55–
Normal	2	8	15	10	3	3
Diabetic	0	0	2	7	7	4
Diabetic as % of total in each age-group	0	0	12	41	70	57

Investigated	61	Untraced	25
Refused	10	Known to have died	2
	Total 98		

The height and weight of each patient were recorded, as were the obstetric history and the presence of a family history of diabetes.

50 g. oral glucose-tolerance tests were carried out after an overnight fast, estimations being made before and at thirty-minute intervals for two hours after the glucose drink. Blood-glucose was determined on capillary samples of blood, by Hoffman's technique (1937), using the Technicon 'Auto-analyser'. This method gives a true glucose figure comparable with the Nelson (1944) and Somogyi (1945) methods.

There is no agreement on what constitutes a standard glucose-tolerance test. The present method is that commonly used in this country (Lawrence 1947, Dische et al. 1958), and differs from those advocated by Wilkerson et al. (1960) and Conn (1958), in which larger amounts of glucose are used and determinations are made on venous blood. Partly because of these differences in method, there is a similar lack of unanimity on the interpretation of results. We have regarded diabetes as definite if blood-glucose levels exceeded 180, 160, and 120 mg. per 100 ml. at one, one and a half, and two hours respectively, and as suspect if two of the three levels exceeded these figures. These criteria are similar to those advocated by Kenny et al. (1951) whose methods were the same, and are comparable with those suggested by Jackson (1952) and Conn (1958).

Results

20 of the 61 patients examined had abnormal glucose tolerance; of these 10 were definitely diabetic, 10 probably so, and 41 normal. Of the 10 women with definite diabetes, only 1 was a known case; she was receiving insulin. 3 of the others had mild symptoms suggestive of diabetes of recent onset.

TABLE II—WEIGHT OF DIABETIC AND NORMAL GROUPS COMPARED

—	Normal (lb.)	Diabetic (lb.)
Mean	166·0	169·5
Standard deviation	30·6	45·2
Range	108–225	70–278
Over 120% of average weight:		
Kemsley (1953)	46%	49%
Lowe and Gibson (1955)	41%	40%

The difference of 3·5 lb. between mean weights is not significant.

It is of interest to compare other findings considered relevant to the pathogenesis of diabetes in the 20 women with definite or probable diabetes with the 41 in whom the glucose-tolerance test was normal.

Age

The mean age of those with normal tests was 43·6 years, and those with diabetic and probably diabetic tests was 49·9. The difference in mean age of 6·3 years is statistically highly significant ($P = < 0·01$). Table I shows the age distribution in the two groups and the proportions of abnormal tests can be seen to increase with advancing age. Glucose tolerance was normal in all the women aged less than 40; while 26% of those aged 40–49 and 65% of those aged 50 and over were abnormal.

Weight

Table II compares the mean body-weights in the two groups. The normal and the diabetic woman are equally obese: compared with Kemsley's (1953) national figures for all women of the same age and height, nearly half of all those examined were overweight. Since mean weight is greater in married than in single women, and increases slightly with parity, a fairer basis for comparison is provided by the data of Lowe and Gibson (1955) for the mean weight of married Birmingham women who had borne three children. Compared even with these standards 40% of both the normal and diabetic groups were obese (table II).

Parity

This is defined as the number of children born alive. Table III compares the percentage distribution of parity

TABLE III—PERCENTAGE DISTRIBUTION OF PARITY

Parity group	Big babies		Parous married women in general population (1951 census)
	Normal	Diabetic	
1	0	0	33
2	17	10	30
3	17	5	16
4	32	10	9
5+6	17	20	7
7+	17	55	4

The stillbirth-rate was also estimated, and no difference was found between either of the groups studied and the general population.

in the normal and diabetic women who had had big babies with a comparable group of women from the general population. This latter figure was derived from the Fertility Report (1959)—based on the 1951 census—for married women aged 45–49 who had borne at least one child. Evidently, women who have had big babies are highly parous compared with the general population.

The diabetic women had a total of 136 live children, and those with normal glucose tolerance 190. The mean parity of the former was 6·8 and of the latter 4·6. The difference in parity of 2·2 children is significant ($P=0·01$), but it can be explained by the fact that more of the diabetics had completed their childbearing years. Thus, when women under 45 are excluded from both groups, the difference in parity between the diabetics (7·1) and the normals (6·1) is no longer significant.

Family History of Diabetes

This is defined as a known history of diabetes in relatives of the 1st and 2nd degree. 37% of the women with normal glucose-tolerance tests had a family history of diabetes. Now, since we have found that 32% of all diabetic women give a family history of diabetes at the time of diagnosis, a hereditary tendency to diabetes appears to be just as strong in women who have borne big babies but are not yet diabetic as it is in women with established diabetes. Curiously enough, only 15% of the group with abnormal glucose tolerance gave a positive family history. The small numbers make the significance of this difference impossible to assess.

Discussion

Previous predictions of the likelihood of diabetes developing in women who have had big babies are, for a number of reasons, of doubtful significance (Kriss and Futcher 1948, Hoet 1954); because only women already known to be diabetic have been considered, calculations have been based on recollected birthweights only, and assumptions have been made regarding the parity of diabetic and normal women which have subsequently proved untenable. These criticisms do not apply to the work of Pedersen (1960), who has followed up a large number of women 15–25 years after they had given birth to a large baby in a Copenhagen hospital. Since the reasons for admission of his cases to hospital are not stated, however, it is difficult to estimate the possible bias towards selecting women likely to develop diabetes by including those with bad obstetric histories and extremes of parity. There is up to now no study of a whole population which assesses the prevalence of diabetes in a random sample of women who have had big babies.

An investigation such as ours can only be conclusive if all the subjects are kept under observation until the time of death, and are compared with a control sample of women of equal parity who had not given birth to large children. Nevertheless, some significant facts do emerge. The most striking of these is the high incidence of abnormal glucose tolerance—of the 34 women, aged 45 and over, more than half were abnormal. It is known, on the one hand, that the incidence of diabetes increases sharply in women after the age of 45 (Pyke 1956, FitzGerald, Malins, O'Sullivan, and Wall 1961); and, on the other, that there is no impairment of glucose tolerance in non-diabetic subjects with increasing age (Mosenthal and Barry 1950). It seems reasonable to presume that at least half of the women who are now normal will become diabetic in the next ten years; and, since the incidence of diabetes continues to remain high up to the age of 75, the proportion who will ultimately develop diabetes can be expected to be very high indeed. That many of the women whose glucose tolerance is at present normal are destined to become diabetic is also supported by the fact that they showed many characteristics known to precede diabetes. About half of all the women examined were overweight (table II), a finding previously noted by Gilbert (1949) and Jackson (1952); and obesity is thought to be an important predisposing influence in the development of diabetes (Joslin et al. 1959). Both the normal and the diabetic women were highly parous (table III), and multiparity has been shown to be associated with an increased incidence of diabetes in later life (Munoe et al. 1950, Pyke 1956, FitzGerald et al. 1961). Finally, a third of the women gave a family history of diabetes, a similar proportion to that found in women with newly diagnosed diabetes.

The results leave unanswered the significance, in the ætiology of diabetes, of giving birth to a large child. An excess of growth hormone might be an important common factor in the production of both phenomena (Gilbert 1949). The present work has shown that having a big baby can rarely be isolated from obesity and multiparity. The difficulties of finding sufficient numbers of women who have borne big babies and yet are both thin and of low parity are very great. We are, therefore, at present ascertaining the prevalence of diabetes in obese and highly parous women who have had babies of normal size, and we hope in this way to assess the separate significance of each of the three factors.

Summary

Glucose-tolerance tests were carried out on 61 women thirteen years after they have given birth to a baby weighing over $10^1/_2$ lb. The women were selected at random from all those who had borne such children in Birmingham in 1947.

20 of the women had definite or probable diabetes.

Though abnormal glucose tolerance was rare under the age of 45, over half of those examined over 45 were abnormal.

Both the normal and diabetic women were obese, highly parous, and often had a relative known to have diabetes.

Probably, therefore, many of the women who were now normal were destined to develop diabetes, but the separate influence of having a big baby could not be assessed in isolation from other factors known to dispose to diabetes.

We should like to thank Prof. Thomas McKeown and Dr. C. R. Lowe for kindly allowing us access to their records, Miss E. Bentley and Miss B. P. Dooley for help with home visiting, and Dr. R. Gaddie for numerous blood-glucose determinations. One of the authors (M. G. F.) was in receipt of grants from United Birmingham Hospitals Endowment Fund and the British Diabetic Association.

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BIRTHWEIGHT OF CHILDREN OF DIABETIC FATHERS

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IT has been known for a long time that many pregnancies of diabetic and prediabetic mothers end in stillbirth, and that many of their babies are overweight. Several explanations have been proposed, such as the effect of maternal hyperglycæmia on the infant's insulin production, excessive maternal production of adrenal steroids, and the effect of maternal growth hormone. Jackson (1952) suggested hereditary factors; and he studied the incidence of large babies among the children of diabetic *fathers*.

In a group of 235 children of diabetic fathers in South Africa he found an incidence of birthweights over 10 lb. (as reported by the fathers) of 13%, compared with 5·4% in a control group. He repeated the investigation in Boston, U.S.A.; and there he noted an incidence of 7·4% in the "diabetic" group, and 3·2% in the control group (Jackson 1954). The excess of large babies is not as great as in prediabetic mothers; and Jackson suggests that hereditary factors are responsible for part of the increase, and the maternal environment for the remainder. In his paper no indication is given of the number of fathers in each group unable to remember a birthweight for their children, and the large babies are therefore shown as a percentage of babies of stated weight, rather than of all babies born to a group of diabetic fathers. It is likely that the weight of abnormally large infants will be remembered more distinctly than that of normal children. Thus if for some reason the proportion of babies of unknown weight were greater in the diabetic group, there might

TABLE I—AGES OF DIABETICS WHEN DIAGNOSED, AND AGES OF DIABETICS, CONTROLS, AND CHILDREN AT TIME OF INTERVIEW

Age	Diabetics and controls at time of interview	Diabetics at time of diagnosis	Children at time of interview with parent	
			Diabetic	Control
0–9	..	..	25 (15·5%)	35 (17·5%)
10–19	..	2	45 (28%)	46 (23%)
20–29	6	18	45 (28%)	62 (31%)
30–39	18	23	37 (23%)	50 (25%)
40–49	27	24	9 (5·5%)	7 (3·5%)
50–59	40	32	..	..
60–69	26	18	..	..
Total	117	117	161 (100%)	200 (100%)

be an apparent excess of large babies if the findings are shown as a proportion of known weight, but, if expressed as a percentage of all babies, the diabetics might not differ from the control group. On the other hand, there were fewer babies under 8 lb. in the diabetic group, suggesting an increase in the mean birthweight rather than exaggeration; and there seems little reason why diabetics should have less accurate memories of their children's birthweights than other people.

Pirart (1955) stated: "confirming Jackson's data (1952, 1954), we saw that children of a diabetic father born to a non-prediabetic woman are often heavier than offspring from a normal father ($P < 0.01$)"; but unfortunately the data on which this statement is based are not given.

Recently Babbott, Rubin, and Ginsberg (1958) further investigated this problem; and they could find no difference between the birthweights of the children of a group of 167 diabetic men, and a control group of 157 men attending a dental department. There is, however, some suggestion in this paper that the control group may not have been strictly comparable with the diabetic group. The total conceptions in the diabetic group were 553, compared with only 356 in the control group; this excess is surprising since the authors mention the high incidence of impotence among the diabetics. Moreover, despite this increased total number of conceptions, the rate of "conceptions per year of exposure" calculated from "the number of years of cohabitation without contraception prior to the age of 45 for the husband and 40 for the wife" was similar

TABLE II—SIZE OF FAMILY

Marital status	Children in family	No. of diabetics	No. of children	No. of controls	No. of children
Single	None	12	..	11	..
Married	None	25	..	17	..
	1	26	26	32	32
	2	36	72	32	64
	3	11	33	13	39
	4	5	20	5	20
	5	2	10	2	10
	6	..	..	2	12
	7	..	..	2	14
	8	..	..	..	..
	9	..	..	1	9
Totals		117	161	117	200

in the two groups. It appears that the diabetics were either considerably older than the controls, or much less inclined to use contraceptives. The paper also related the number of big babies to the number of those of known weight, rather than to the total number of babies. Finally, though the difference was not significant, there was in fact a small excess of large babies among those with diabetic fathers, 5·7% being over 10 lb., compared with 4·1% in the control group.

In view of the conflicting evidence in the few papers published, the possible sources of error, and the importance of fœtal gigantism in the children of diabetics, I report the result of a similar investigation carried out in this country.

Material and Methods

120 men between the ages of 20 and 70 attending the diabetic clinic at the Central Middlesex Hospital were asked for details of the number, age, and birthweights of their children. The father was weighed at interview, and his greatest known weight was recorded, also the age when diabetes was diagnosed. These details were obtained from 117 men. Similar details were obtained from a control group of 117 men, matched for age by decades, under my care in other outpatient departments in the hospital (most of them in a gastroenterological clinic). The reason for choosing this particular control group was that, since the incidence of impotence was being compared, it was felt important that the investigator-patient relationship should be the same in the two groups, if accurate information was to be obtained. For simplicity, the few men who had married more than once were excluded.

As might have been expected, many answers were very imprecise.

Weights expressed as "average", "not very big", &c., have been included in the "not known" group, as have statements like "between 6 and 8 lb.". But where a figure was given which could be classified within 1 lb.—e.g., "between 7 and 8 lb."—this was entered as less than 8 lb. and more than 7 lb. As there were many such imprecise figures, the two groups were scrutinised by an independent observer, who did not know the group to which they belonged, and who classified the figures as indicated.

To check the accuracy of the statements, a letter was subse-

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TABLE III—BIRTHWEIGHTS OF CHILDREN OF DIABETICS AND CONTROLS

Weight of baby (lb.)	No. of diabetics	No. of controls
Unknown	27	20
Under 5	3 } 6	9 } 17
5	3 }	8 }
6	19	29
7	50	65
8	30	56
9	17	9
10	7	4
11	3 }	0 }
12	1 } 5	0 } 0
Over 13	1 }	0 }
Total no. of children	161	200

quently sent to all the men who had said that 1 or more of their children had weighed 10 lb. and over at birth, asking them to check the weight with their wives. Answers were received from 6 of the 8 diabetic fathers concerned, and from all 4 control fathers. 1 "diabetic" child and 1 "control" child were stated to be under 10 lb. at this re-check, the father having previously reported a greater weight; but in addition 1 diabetic father mentioned another child weighing over 10 lb. who had not been recorded at the first interview. Thus this limited check provided no evidence of any easily rectifiable errors affecting one group more than the other, and the results of the original survey have been given without correction.

Results

It will be seen that the diabetic fathers had rather fewer children than the controls. This, coupled with the absence of very large families in the diabetic group, suggested that the deficiency might be due to the onset of impotence in middle-aged diabetics.

The stated birthweights of the two groups are shown in table III.

The reason why more diabetic fathers are unable to give a birthweight for their children is obscure, and may reflect some different emphasis in questioning the two groups. The proportion of children with diabetic fathers varies directly with the birthweight; and if the trend is taken into account, the differences between the proportions are statistically highly significant (χ^2 for the regression = 9·07, $n = 1$, $P < 0{\cdot}01$). In the figure the weights are expressed as a percentage of those of known weight for comparison with the data in the papers discussed. For the reasons given above, this may have slightly increased the difference between the two groups.

It is possible that the build of the father might be related to the size of the baby; and as might have been expected, the diabetic men were considerably heavier than the controls, when weighed at interview, and according to their stated "greatest known weight". (The latter, though an unconfirmed statement is relied upon, is a better guide to body-build than the weight at interview, since it excludes the effects of therapeutic weight reduction in the diabetics, and weight loss from ill health among the controls.) There was, however, no correlation between the father's weight and child's birthweight ($R = +0{\cdot}003$).

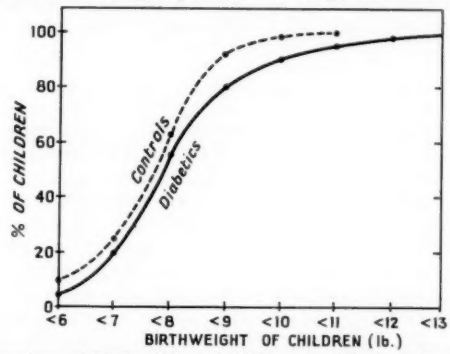
The proportion of large babies does not tend to increase as the time when diabetes is diagnosed approaches. In fact, contrary to the findings in women, the proportion of large babies is *greater* in the fathers with a long interval between the birth of the child and the diagnosis of diabetes. This could be due to the greater age of the men with a longer prediabetic history, and possibly a greater tendency to exaggerate as memory gets less accurate; but the ages of the children of diabetics are strictly comparable with those of the controls (table I), and thus the length of time is the same for the two groups.

TABLE IV—TIME WHEN FATHER'S DIABETES WAS DIAGNOSED AND WEIGHT OF BABY

Baby's weight	Period before diagnosis of diabetes			After diagnosis
	Over 20 yr.	10–20 yr.	Less than 10 yr.	
9 lb. and over	17	7	3	2
Under 9 lb.	35	25	33	12
Not known	11	9	4	3
Total ..	63	41	40	17

Discussion

It is obvious that the fathers' statements on their children's birthweights are often highly inaccurate. I was embarrassed to find my own memory on this point extremely unreliable. It is probable, as Jackson noted, that there is a universal tendency to exaggerate the birthweight; but it is difficult to understand why the diabetic fathers should exaggerate more than the controls. It is possible that the diabetics might regard big babies more highly than the controls; but there is no evidence that this was so. Both groups in the investigation were drawn from the local population served by a district hospital, and, as far as could be judged, came from similar social backgrounds.



Comparison of birthweights of children of diabetic fathers with those of controls.

It therefore appears that the difference between the two groups is real, and that Jackson's finding, that the children of present and future diabetic fathers tend to be heavier than the average is confirmed. The difference is not explained by a difference in the fathers' builds, and is unrelated to the onset of clinical diabetes. A possible explanation could be that diabetics and future diabetics tend to marry women who are also potential diabetics, and who will therefore produce heavier babies. In fact in only 1 wife of a diabetic has diabetes developed so far; but this marriage was responsible for 1 of the big babies. In none of the wives of the control fathers was diabetes known to have developed by the time of the interview. Thus the incidence of diabetes in the wives is lower, for both the diabetics and the controls, than that in the general population. It does not seem likely, therefore, that unsuspected prediabetes in the wife could be responsible for these large babies.

Summary

117 diabetic men and 117 controls of the same age-distribution were asked the birthweights of their children. The diabetics had fewer children (161) than the controls (200); but more were heavy. Thus there were 12 children weighing over 10 lb. and 29 over 9 lb. among those of diabetic fathers, compared with 4 and

13 respectively in the larger group of those of the controls. This difference is not related to differences in build in the two groups.

The tendency to produce heavy babies and the time of onset of the diabetes were not directly related. No reason why memory should be more inaccurate in the diabetic fathers could be established.

My thanks are due to Dr. P. H. Friedlander for assistance in collecting the data, and to Dr. Richard Doll for much helpful advice and criticism.

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MEDIASTINAL LYMPHATIC GLAND TUBERCULOSIS IN ASIAN AND COLOURED IMMIGRANTS

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SINCE the end of the late war there has been a considerable increase in the numbers of immigrants to the United Kingdom from Asia, Africa, and the West Indies, who now number 200,000. This paper gives an account of seven patients from India and the West Indies who attended hospital with tuberculosis of a pattern unfamiliar in this country. Their chest radiographs showed mediastinal glandular enlargement with or without associated parenchymal lesions. Tubercle bacilli were not readily demonstrated, and the initial diagnoses included sarcoidosis, carcinoma of the bronchus, reticulosis, and pneumonia. So likely did the diagnosis of carcinoma of the bronchus seem in one patient that radiotherapy was given. Another was thought to have lymphadenoma, and received a course of corticosteroids without antituberculous drugs.

Case-reports

Case 1.—A 34-year-old West Indian bus conductor from Dominica, who had been living in the United Kingdom for 15 months, presented with 3 weeks' history of high fever, cough, and sputum. His chest radiograph showed considerable bilateral hilar adenitis and patchy left lower-zone consolidation (fig. 1). The Mantoux test (100 T.U.) was negative, and the sputum contained no tubercle bacilli. After 2 months in hospital his general symptoms had improved and the Mantoux test (10 T.U.) was positive. He was finally discharged with a provisional diagnosis of sarcoidosis.

8 months later his symptoms returned, and radiography showed extensive infiltration in the left lung, greatest in the upper and mid zone, partially obscuring the left hilum. The sputum now contained tubercle bacilli, resistant to isoniazid. He was treated with antituberculous drugs, and 9 months later there was complete clearing of the lung-fields, but still a suspicion of right hilar enlargement.

Case 2.—A 47-year-old male Sikh factory-worker from India, who had been living in the United Kingdom for 6 years, presented with 5 weeks' history of remittant pyrexia (102–103°F), cough, occasionally blood-streaked sputum, and loss of weight. The chest radiograph showed enlarged glands at the right hilum and partial atelectasis of the apical segment of the right lower lobe. No neoplastic cells or tubercle bacilli were found in the sputum. Bronchoscopic examination showed widening of the carina, and compression and rigidity of the right lower-lobe bronchus, with some irregularity of the mucosa. A biopsy specimen showed squamous metaplasia. He was thought to have an inoperable carcinoma and was given radiotherapy to the hilar glands. Subsequently, sputum cultures were positive for tubercle bacilli, and a scalene-node biopsy specimen showed active tuberculosis. He was treated with antituberculous drugs, and radiography showed gradual resolution of the right hilar glands, leaving some residual fibrosis.

Case 3.—A 16-year-old schoolgirl from St. Vincent, West Indies, who had been living in the United Kingdom for 5 months, presented with a month's history of malaise and remittent pyrexia (102°F). The Mantoux test (1 T.U.) was positive. Radiography showed some calcification of the right hilar glands with very slight associated fibrosis. After extensive investigations for her pyrexia she was given a trial course of *p*-aminosalicylic acid (P.A.S.) and isoniazid, and within 24 hours her temperature fell to normal. Treatment was therefore continued for 6 months. A year later, however, her symptoms recurred. The liver and spleen were palpable and tender, and radiography showed bilateral enlargement of the upper mediastinal glands (fig. 2). A scalene-node biopsy specimen showed caseating tuberculosis, and the sputum contained tubercle bacilli. Antituberculous treatment was started again, with immediate clinical improvement. During 2 years' treatment radiography showed gradual decrease in the size of the mediastinal glands.

Case 4.—A 28-year-old ship's steward from the West Indies, who had been living in the United Kingdom for 9 years, presented with pyrexia. All investigations were negative, except the chest radiograph which showed enlarged right hilar

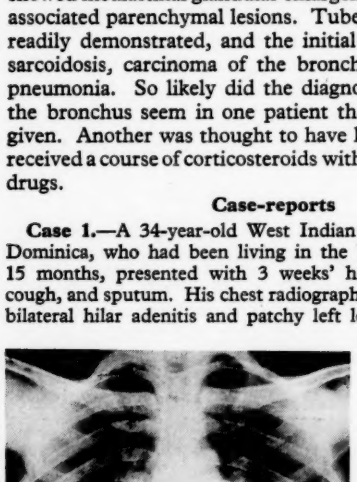

Fig. 1—Case 1. Chest radiograph showing bilateral hilar adenitis and patchy left lower-zone consolidation.

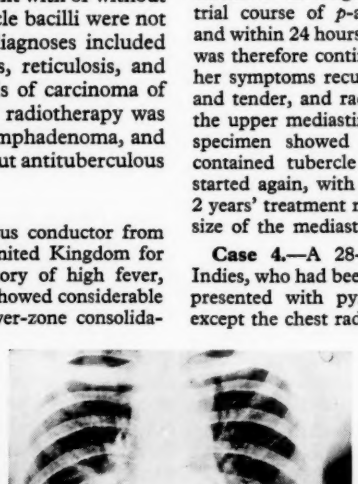

Fig. 2—Case 3. Chest radiograph showing bilateral enlargement of the upper mediastinal glands and calcification of the right hilar glands with very slight associated fibrosis.

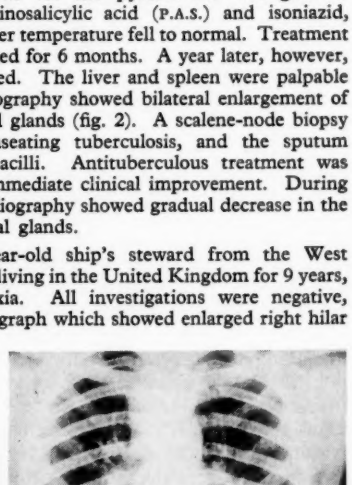

Fig. 3—Case 6. Chest radiograph showing right paratracheal glandular enlargement.

glands. He was treated empirically with chlortetracycline, and his temperature gradually fell to normal, but the hilar enlargement did not resolve. 7 months later he developed cough and fever, and radiography showed consolidation of the right lower lobe. The sputum contained tubercle bacilli. He was treated with streptomycin and isoniazid daily for 11 weeks resulting in sputum conversion, but he then discharged himself from hospital. A year later he had enlarged right axillary glands which were excised and showed fibrocaseous tuberculosis. 4 years later he again had high fever, and the chest radiograph showed further right hilar-gland enlargement with associated collapse and consolidation in the right upper lobe. His sputum contained tubercle bacilli. After antituberculous treatment for 21 months, radiography showed some distortion of the right hilum with adjoining fibrosis and a little right upper-zone infiltration.

Case 5.—A 27-year-old male packer from India, who had been living in the United Kingdom for 4 years, presented with cough, sputum, shortness of breath, and pyrexia, and was found to have a right pleural effusion. No tubercle bacilli were recovered, but a Mantoux test (10 T.U.) was positive, and he was treated with antituberculous drugs. His effusion cleared in a few weeks but enlargement of the left hilar glands and a mass in the anterior segment of the left upper lobe then became apparent. Later he developed enlarged cervical lymph-glands which on excision contained acid-fast bacilli and were histologically tuberculous. Subsequently, the sputum was positive on culture for tubercle bacilli. After 18 months' treatment his chest radiograph was unchanged.

Case 6.—A 24-year-old male suitcase-maker from the West Indies, who had been living in the United Kingdom for 3 years, had persistent pyrexia and slight cough while in hospital with a duodenal ulcer. Radiography showed right paratracheal glandular enlargement (fig. 3). Lymphadenoma seemed the most probable diagnosis, and treatment was started with tretamine and prednisone. Within 3 weeks his chest radiograph showed extensive infiltration and cavitation in both upper lung-fields, and the sputum was positive for tubercle bacilli on direct examination. On treatment with antituberculous drugs the lung-fields cleared rapidly and the paratracheal enlargement gradually disappeared.

Case 7.—A 24-year-old male textile worker from India, who had been living in the United Kingdom for a year, presented with 2 months' history of sore throat, pyrexia (102°F), cough, scanty sputum, wheeziness, and shortness of breath. The tip of the spleen was palpable. Radiography showed gross enlargement of the right paratracheal glands, and tomography confirmed this and showed widening of the carina and narrowing of both main bronchi (fig. 4). The sputum was negative for tubercle bacilli on direct examination and culture. Bronchoscopic examination showed widening of the carina and a saddle-shaped red granular mass partially occluding both main bronchi. A biopsy specimen showed tuberculous granulation tissue covered by squamous epithelium. Treatment was started with antituberculous drugs, and rapid clinical and radiological improvement followed.

Fig. 4—Case 7. Tomograph showing widening of the carina and narrowing of both main bronchi.

Discussion

In these seven patients the main presenting symptom was pyrexia, with some cough and sputum. In most of them the illness was long with a tendency to relapse. In every case the diagnosis was finally confirmed by the demonstration of tubercle bacilli or by histological proof of tuberculosis. Obvious enlargement of the hilar glands was observed on one side in three patients and on both sides in one. The paratracheal glands were enlarged on the right side in two, and there was bilateral enlargement of the upper mediastinal glands in one. Bronchoscopic examination in two patients showed changes simulating carcinoma with widening of the carina due to subcarinal glands.

The glandular enlargement did not show any dramatic response to streptomycin, P.A.S., and isoniazid in various combinations. This was similar to the experience of Bentley et al. (1954) in treating primary tuberculous hilar adenitis in European children. At the end of the period of observation the mediastinal glands in one patient were unchanged, in three were reduced in size, and in one had resolved; while two patients showed distortion of the hilum due to fibrosis in the adjoining lung. Cervical glands developed during antituberculous treatment in case 5, and axillary glands some months after a relatively short course of treatment (11 weeks) in case 4. The pulmonary infiltration, however, responded satisfactorily to treatment.

Are the enlarged mediastinal glands in Asian and coloured adults due to primary tuberculosis? Opie (1930) thought that the lesions in adult Jamaicans resembled primary tuberculosis in European children and that they were due to primary infection occurring in adult life in subjects who had previously escaped infection. This view was later opposed by Long (1937) and Pastor (1937) on the grounds that studies in various parts of America and in Puerto Rico indicated that, in the same area, a higher proportion of coloured than white children were tuberculin-sensitive; furthermore, it did not explain why enlarged glands should occur only in coloured adults. The same argument applies to immigrants from India and the West Indies living in the United Kingdom.

Benjamin (1956) quotes the percentage of positive tuberculin reactors at the ages of 7 to 14 as 18% in Jamaica (1951–53), 24% in Trinidad and Tobago (1952–54), and 16% in Windward Islands and Grenada (1954). In the same age-group in Pakistan (1951–54) 40% were positive, and in India (1955) 47% of children living in towns and 35% of those living in villages were positive. As in 1955 14% of London schoolchildren were tuberculin-positive at the age of 13 (London County Council 1956), it seems certain that immigrants have not been coming into a more heavily infected area.

The disease seen in our patients resembles primary tuberculosis in European children in certain respects. Enlargement of the mediastinal glands is common in children, but usually one side only is affected. Bentley et al. (1954) found bilateral mediastinal-gland enlargement in only 35 of 202 children with simple primary tuberculosis. In our series of seven patients both sides were affected in two, one with hilar and another with upper-mediastinal glands. In European children calcification is common in the healing of tuberculous mediastinal glands, and usually begins about a year after infection. In our series, six of whom were kept under observation for more than a year, calcification was not seen except in one in whom it was previously present. This patient (case 3) developed enlarged bilateral upper mediastinal glands

after calcification at the right hilum had been present for at least a year. Another (case 5) showed hilar gland enlargement after clearing of a pleural effusion on the opposite side. Wallgren (1948) observed that pleural effusion usually takes place 3 to 7 months after the primary infection and usually on the same side; but in our patient the effusion and the glands were on opposite sides, and the glands followed the effusion. Our findings suggest that, though enlarged mediastinal glands in Asian and coloured adults may develop at the time of the primary infection, the mediastinal adenitis may also occur at a later stage of the disease, which is uncommon in Europeans.

Pinner and Kasper (1932) in postmortem studies on Negroes found caseous lymph-glands, even in adults with calcified primary lesions, and concluded that tuberculosis in the Negro produces a high state of allergy but not an increased resistance. Our observations support the view that some Asian and coloured adults fail to develop the same degree of acquired resistance as the European at the time of primary infection, so that the subsequent clinical picture may present features of both primary and chronic pulmonary tuberculosis simultaneously.

In conclusion, the finding of enlarged mediastinal glands in an Asian or coloured patient should immediately suggest the possibility of tuberculosis; otherwise there may be unnecessary errors and delays in diagnosis.

Summary

Seven patients from India and the West Indies with mediastinal lymphatic gland tuberculosis are described.

The main presenting symptom was pyrexia, together with some cough and sputum. The course of the illness was long with a tendency to relapse. The radiological appearances were those of mediastinal glandular enlargement, either unilateral or bilateral, with or without associated parenchymal lesions. The enlarged mediastinal glands showed only gradual response to antituberculous drugs, compared to the more rapid response of the parenchymal lesions.

The relation of enlarged mediastinal glands in Asian and coloured adults to primary tuberculosis is discussed. Our findings suggest that, though the mediastinal adenitis may develop at the time of the primary infection, it may occur at a later stage of the disease, which is uncommon in Europeans. Failure to acquire resistance at the time of the primary infection may account for a clinical picture presenting features of primary and chronic pulmonary tuberculosis simultaneously.

The finding of enlarged mediastinal glands in an Asian or coloured patient should immediately suggest the possibility of tuberculosis.

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EXCRETION OF PORPHOBILINOGEN AND δ-AMINOLÆVULINIC ACID IN ACUTE PORPHYRIA

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ACUTE porphyria is an inborn error of metabolism characterised by attacks of abdominal pain which may be slight, or of such severity as to simulate a surgical emergency, often in association with neurological and mental symptoms and signs of great variety. During the acute stages, the monopyrrolic compound, porphobilinogen (P.B.G.) is excreted in the urine (Waldenström 1937); and, as has subsequently been shown by Granick and vanden Schrieck (1955), this is accompanied by its metabolic precursor, δ-aminolævulinic acid (A.L.A.). The P.B.G. excretion during remission may either decrease to low or negligible amounts (Waldenström 1937, 1957), or, according to Watson (1954), continue in about 20–50% of the quantities excreted during the acute stage.

In the patient studied by Granick and vanden Schrieck, the rate of excretion remained high during periods in which mild symptoms or no pain at all were observed, and the onset of pain was not related to increased P.B.G. excretion. This patient excreted about 40 mg. of A.L.A. daily—i.e., about 40% by weight of the excreted P.B.G. Lowry et al. (1950) had found P.B.G. in each of 44 subjects with porphyria, 16 of whom were also investigated during remission. 15 of the 16 excreted P.B.G. in more than trace quantities; and in 7 cases in which serial observations were made, the P.B.G. excretion decreased substantially during complete clinical remission. Watson et al. (1951) emphasised that the P.B.G. reaction sometimes became negative during remission, but the qualitative test they used was less sensitive for the detection of slightly increased amounts of P.B.G. than the quantitative measurements by the method of Mauzerall and Granick (1956). Using this method Haeger (1958) determined P.B.G. and A.L.A. in the urine of 34 patients with manifest porphyria, and in 128 of their close relatives. Contrary to the earlier report of Hammond and Welcker (1948) who investigated 1000 non-porphyric patients without finding P.B.G. in the urine, Haeger found small amounts of P.B.G. as well as of A.L.A. in normal urine. She showed that all the 34 patients with the overt condition excreted P.B.G. in pathologically increased amounts, and, of these, 29 also excreted increased quantities of A.L.A. Of 7 "genetically certain carriers"—i.e., persons whose parent, brother, sister, child, niece or nephew had either latent or manifest porphyria—6 excreted increased amounts of both A.L.A. and P.B.G. while in the 7th P.B.G. only was increased.

The present study was undertaken to investigate the possible correlation between variations in the A.L.A. and P.B.G. output and changes in physical and mental state.

TABLE I—EXCRETION OF PORPHOBILINOGEN AND δ-AMINOLÆVULINIC ACID IN THE 12 MAUDSLEY HOSPITAL PATIENTS

Case no.	Days of study	Porphobilinogen excreted per day (mg.)	δ-aminolævulinic acid excreted per day (mg.)	Porphobilinogen + δ-aminolævulinic acid excreted per day (μmoles)
7	13	1·4 ± 2·8 (0–10)	2·4 ± 1·9 (1–8)	22 ± 27 (0–105)
5	28	1·6 ± 4·5 (0–23)	3·6 ± 0·1 (2–7)	37 ± 25 (15–148)
1	11	7·1 ± 3·2 (2–10)	5·5 ± 2·0 (3–9)	72 ± 29 (28–113)
8	17	13·9 ± 5·4 (4–26)	4·0 ± 1·5 (1–7)	91 ± 35 (18–161)
12	21	4·2 ± 2·5 (0·3–7·9)	9·6 ± 2·8 (0·5–15·3)	92 ± 29
2	11	44 ± 8 (31–59)	14 ± 6 (1–22)	301 ± 66 (192–439)
11	9	58 ± 16 (43–92)	14 ± 9 (7–36)	360 ± 134 (281–682)
9	10	65 ± 8 (52–78)	23 ± 5 (17–29)	462 ± 56 (360–518)
10	34	49 ± 21 (15–132)	32 ± 32 (5–74)	465 ± 156 (133–724)
3*	9	60 ± 34 (8–137)	46 ± 24 (2–86)	498 ± 246 (160–990)
3†	13	71 ± 23 (43–118)	54 ± 14 (30–74)	726 ± 197 (499–1089)
4	15	66 ± 32 (19–127)	32 ± 14 (11–57)	735 ± 303 (191–1267)
6	6	113 ± 17 (84–133)	56 ± 6 (48–64)	934 ± 110 (738–1042)

* Remission. † Attack.

At the same time the opportunity was taken to examine in detail the previous personality and life history of the porphyric patients, and these findings will be reported elsewhere (Ackner et al. 1961).

The Patients

12 patients known to have suffered from acute porphyria were admitted to the Maudsley Hospital for a period of two weeks or more for investigation. All except 2 (cases 5 and 12) who had recurring attacks of a doubtful nature, were in the latent stage on first admission; but 1 (case 3) was subsequently readmitted in an acute attack, and 3 (cases 4, 6, and 10) had acute symptoms after admission to hospital. 2 further patients were studied, both apparently in the early recovery stages of a severe acute attack—1 (case 13) in Lewisham Hospital under the care of Dr. J. Staffurth, and the other (case 14) in King's College Hospital under the care of Dr. J. C. Hoyle. This last patient was readmitted in an acute attack and was again studied until he was well enough to return home. The clinical features of these patients are summarised in the appendix.

Chemical Methods

P.B.G. and A.L.A. were estimated by the method of Mauzerall and Granick (1956) which depends on the separation of P.B.G. from A.L.A. on an ion-exchange column followed by estimation of the former with Ehrlich's reagent and of the latter with the same reagent after condensation to a monopyrrolic compound with acetyl-acetone.

Results

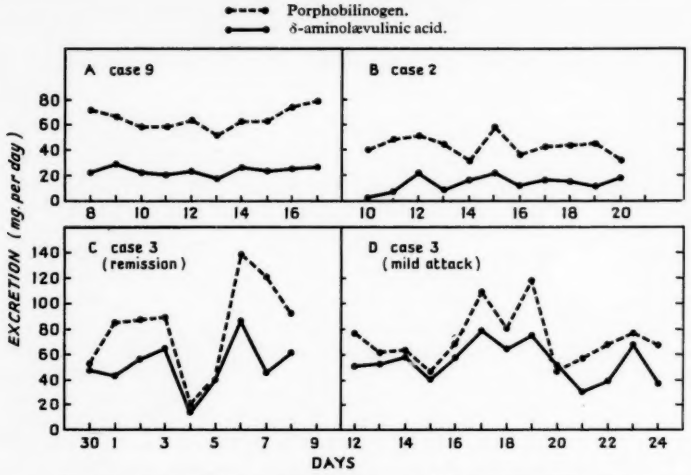
Table I shows the results of the investigations carried out on the 12 patients admitted to the Maudsley Hospital, with the mean excretion of P.B.G. and A.L.A. in ascending order of the combined excretion of these two compounds in micromoles. The sum of the excretions of A.L.A. and P.B.G. has been given in micromoles because of the different molecular weights of these two compounds. The 4 patients with the highest average excretions of A.L.A. and P.B.G. combined (cases 3, 4, 6, and 10) all experienced, during the period of investigation, attacks of abdominal pain which were probably due to exacerbations of the porphyria. But 3 other patients (cases 2, 9, and 11) also had high average excretion-rates; and, although 1 (case 2) had some residual paralysis, none complained of any symptoms during the investigation and their last porphyric attack had been some time previously. 2 patients (cases 5 and 12) who were admitted complaining of abdominal pain excreted P.B.G. and A.L.A. in amounts little exceeding normal, but in both there were features suggesting that their complaints might be largely of psychological origin. Cases 1, 7, and 8 were free from symptoms, and the mean excretions of P.B.G. and A.L.A. were scarcely raised above the normal given by Haeger (1958) although there were fluctuations giving peaks of between two and three times the upper limit of normal.

Table II shows the results obtained in the 2 subjects who at the time of investigation had severe symptoms either of pain or of frank paralysis. Case 13 was first studied about fourteen days after the beginning of an acute attack. Despite this, the average excretion of P.B.G. and A.L.A. was lower than in the almost symptomless patients who were excreting considerable quantities of these compounds. Case 14 was first studied when he was recovering slowly from an acute attack which had occurred several weeks previously. He was then excreting less P.B.G. and A.L.A. than case 6, who, of the other subjects studied, excreted the largest amounts of these two compounds. However, two days after his discharge from hospital, reasonably well, he experienced an acute attack and was immediately readmitted for further investigation. He was then studied for ten days during the acute illness when the mean and peak P.B.G. excretions were 109 and 171 mg. respectively and the corresponding figures for A.L.A. were 87 and 156 mg. During a subsequent period, the mean and peak excretions of P.B.G. were 132 and 250 mg. and of A.L.A. 99 and 156 mg. At this time he seemed dangerously ill, but remission then set in and his excretion of P.B.G. and A.L.A. returned to about their pre-attack levels.

All the subjects studied showed variation in the daily excretion of the two compounds. In some these were relatively small (see figure, A and B) while in others they were much larger (see figure, C); no correlation was discernible between the peaks of P.B.G. and A.L.A. excretion and the clinical condition; and indeed case 3, who was studied on the first occasion during remission and on a second occasion after having had an attack of abdominal pain (see figure, D) showed neither a significant difference

TABLE II—EXCRETION OF PORPHOBILINOGEN AND δ-AMINOLÆVULINIC ACID IN 2 SERIOUSLY ILL PATIENTS WITH ACUTE PORPHYRIA

Case no.	—	Days of study	Porphobilinogen excreted per day (mg.)	δ-aminolævulinic acid excreted per day (mg.)	Porphobilinogen + δ-aminolævulinic acid excreted per day (μmoles)
13	—	15	36 ± 8 (22–51)	25 ± 9 (5–38)	350 ± 96 (157–475)
14	*First admission (remission)*	25	88 ± 13 (66–119)	41 ± 5 (28–54)	705 ± 80 (510–875)
	Second admission (relapse):	10	109 ± 41 (62–171)	87 ± 38 (51–156)	1144 ± 452 (796–1935)
	During treatment with adenosine monophosphate	14	132 ± 56 (59–249)	99 ± 38 (49–156)	1344 ± 524 (635–2182)
	During treatment with zinc	21	89 ± 32 (42–179)	38 ± 15 (24–87)	689 ± 248 (376–1452)
	During remission	9	71 ± 22 (43–109)	53 ± 15 (30–78)	726 ± 197 (478–1089)



Variations in excretion of porphobilinogen and δ-aminolævulinic acid.
A and B demonstrate the relatively minor fluctuations in cases 9 and 2. C and D represent the distinct fluctuations in case 3 during remission and mild attack.

between the mean values nor any obvious change in nature or extent of the variations in excretion of P.B.G. and A.L.A.

Discussion

Relation of P.B.G. and A.L.A. Excretion to Symptoms

In the majority of our patients the diagnosis of acute porphyria had been suggested by the voiding of urine of a colour varying from pale pink to deep mahogany or which had become dark on standing. Porphobilinogen itself is a colourless chromogen, and the freshly voided urine is often of a normal colour even during the acute attacks. The change to the porphyrins and other coloured compounds may occur after acidification and heating or after the urine has been standing for any length of time. The colour of the urine thus depends on physical factors and does not necessarily reflect the concentration of porphobilinogen.

It is the occasional coloured urine that often points to the diagnosis, and it is perhaps this that has led to the widespread belief that the acute attack of porphyria is accompanied necessarily by an increased excretion of porphobilinogen. This view receives little support from the general pattern of our results, although in cases 1–12 excretion of A.L.A. and P.B.G. tended to be greatest in those patients with the more definite symptoms. The mean excretion of A.L.A. and P.B.G. and the peak limits attained during the acute attack of case 14 were the highest observed for all the subjects studied. On the other hand, case 13 was very ill and yet excreted quantities of P.B.G. and A.L.A. much lower than other subjects, who were practically symptomless; and in case 3, who was studied in relapse as well as in remission, the differences between the levels of excretion during the two stages were insignificant; indeed, there were days during the symptom-free period when excretion of P.B.G. and A.L.A. was greater than at any time during the period of relapse. Cases 5 and 12 apparently experienced pain and other symptoms at times when excretion of P.B.G. and A.L.A. was increased little if at all.

Case 2, who had residual weakness and paralysis from attacks several years previously, excreted significantly increased amounts of A.L.A. and P.B.G. although free from pain at the time of investigation. Case 11 was of special interest. He had been free of symptoms for at least three years before investigation, yet on admission he was excreting 92 mg. and 46 mg. of P.B.G. and A.L.A. respectively per day. This level of excretion approaches that of the subjects in relapse, and certainly equals that of such subjects on individual days. The high level soon decreased during his stay in hospital. There is thus no doubt that patients who have had attacks of acute porphyria can excrete A.L.A. and P.B.G. in moderately large amounts while remaining well and free from clinical features of the disease.

The P.B.G./A.L.A. Ratio

In general the excretion of A.L.A. paralleled that of P.B.G., and there was no evidence that the A.L.A. excretion or the combined P.B.G. and A.L.A. excretion reflected the clinical condition any better than did the P.B.G. excretion. The ratio of P.B.G. to A.L.A. must depend on the activity of the enzyme A.L.A. dehydrase responsible for the conversion of A.L.A. to P.B.G. in the tissues. In health this ratio appears to be less than 1, but in patients with acute porphyria, as well as in carriers of the porphyria gene, the ratio usually increases to above 1 (Haeger 1958), presumably reflecting the adaptive increase in the enzyme activity which Scott (1954) has already shown to be present in patients with the disease. In case 14 the ratio fell below unity when he was excreting larger quantities of the precursors at the time of his acute attack. This suggests that at this time the body was suddenly flooded with an amount of A.L.A. which exceeded the capacity of the already greatly increased A.L.A. dehydrase activity.

Excretion of P.B.G. and A.L.A. in the Acute Attack

A severe acute attack might thus be associated for a short period—perhaps a few days or even hours—with the excretion of the two porphyrin precursors in much greater quantities than in the series we have studied. If this were so, the symptoms experienced by many patients might represent the sequelæ of disorder in the nervous system which had occurred earlier at the time of such a "metabolic explosion". None of the Maudsley patients can have had an acute exacerbation of this severity during the period of study. Case 13 at the time of investigation might have been in a stage of slow recovery. On the other hand, case 14, at the times at which his illness was severe, was excreting very much larger amounts of P.B.G. and A.L.A.

TABLE III—PORPHOBILINOGEN EXCRETION IN SERIOUSLY-ILL PATIENTS WITH PORHYRIA

Source	Case	Remarks	Max. P.B.G. excretion (mg. per day)
Rimington (unpublished)	Mrs. Q.	1st attack	248*
		2nd ,,	208
		3rd ,,	417
,,	Miss M.	Severe attack	405*
,,	Mr. E.	..	350*
Goldberg (unpublished	23	Day of death	248*
,,	2	P.M.	195*†
,,	32	P.M.	407*†
,,	43	P.M.	385*†
Gray (1945)	Miss H.	..	500–600†
Kalényi et al. (1960)	..	During attacks	140–160
Waldenström (1957)	..	With colic	73, 39

*mg. per litre urine.
†Calculations from uroporphyrin determined by method of Sveinsson and Rimington (1950). The P.B.G. is assumed to be converted to porphyrin in 20% yield.

than any of the other patients, and there is no doubt that his acute phase was prolonged. Nevertheless, the definition of what constitutes an acute attack is very nebulous. An analysis of published data and of data kindly made available by colleagues suggests that patients with acute porphyria can at times excrete much larger amounts of P.B.G. than we have observed. All 8 patients referred to in table III excreted much larger amounts of P.B.G. while their symptoms were extremely severe. Unfortunately, A.L.A. was not measured in any of these cases. On the other hand Goldberg (1954) has described 2 cases of acute porphyria in which 52 and 250 mg. P.B.G. was excreted daily during brief periods of freedom from pain. He has also described 2 patients excreting 120 and 100 mg. P.B.G.; 1 had recovered fully from a previous attack, while the other never had symptoms referable to porphyria. The P.B.G. content of the specimens of urine removed post mortem from 4 of Goldberg's subjects was probably very high. However, the urine passed the day before death by 1 of his patients, and a postmortem specimen from an unpublished case examined by one of us (C.H.G.), contained only 19·6 and 12 mg. P.B.G. per litre respectively. It cannot, however, be excluded that in these 2 cases terminal renal failure prevented the excretion of P.B.G. in high concentrations in the urine.

It seems unlikely that there can be a direct causal relation between symptoms and P.B.G. and/or A.L.A. excretion. Berlin et al. (1956) found that administration of A.L.A. to normal men, while causing excretion of amounts of A.L.A. and P.B.G. comparable to those occurring in acute porphyria, did not cause the clinical symptoms of the disease. In patients with the disease, A.L.A. did not cause worsening of symptoms. Neither P.B.G. nor A.L.A. can therefore be toxic, and it seems probable that the excretion of the two metabolites and the nervous system changes are separate manifestations of a metabolic event or series of events.

Diagnosis of Acute Porphyria

From the clinical point of view porphyria is a deceptive and frequently misdiagnosed condition. The early symptoms are both varied and variable, and are often unaccompanied by physical signs. Being a rare disorder, it is seldom diagnosed at an early stage. The abdominal pain, vomiting, nausea, and constipation may, even in the absence of pyrexia, leucocytosis, and abdominal rigidity, lead to a tentative diagnosis of a surgical emergency; and an exploratory laparotomy with negative findings usually results in the diagnosis of a functional disorder. Complaints of weakness of the limbs, with variable aches and abdominal pain unassociated with demonstrable physical signs, commonly cause hysteria to be diagnosed; and this diagnosis has been retained even when advanced paralysis due to porphyria has been present for some time. The impression that the complaints of the porphyric patient are functional rather than organic is often reinforced by the accompanying signs of emotional instability; and if these give way to a frankly psychotic state, admission to a mental hospital is the usual outcome. It is therefore proper that the literature relating to the clinical aspects of porphyria should repeatedly contain warnings of the dangers of dismissing certain phenomena as hysterical, and so failing to make the correct diagnosis.

On the other hand, our results indicate that the finding of porphobilinogen in the urine of a patient with suggestive symptoms does not prove the diagnosis of acute porphyria for quite a high excretion-rate may occur in symptomless cases and mild attacks may be accompanied by no increase in output. In 4 of our patients (4, 5, 10, and 12) environmental stress was present; and indeed some workers have claimed that emotional factors can precipitate attacks. Elsewhere we report in detail findings which suggest that in many such patients either the stress is coincidental or the attack itself is largely a hysterical reaction to the stress with the porphyric process playing little or no part (Ackner et al. 1961).

The diagnosis of the mild attack presenting with no demonstrable physical signs is therefore a matter for clinical judgment, often requiring skilled psychiatric assessment.

Summary

The urinary excretion of porphobilinogen (P.B.G.) and δ-aminolævulinic acid (A.L.A.) has been measured and compared with the clinical findings in 14 patients with acute porphyria.

Although there was a rough correlation between severity of symptoms and excretion of P.B.G. and A.L.A., some patients excreting considerable quantities of these compounds were symptomless, while others with no greatly increased excretion of P.B.G. and A.L.A. had symptoms.

The excretion of these two compounds fluctuated considerably, but there was no correlation between peaks of excretion and acute symptoms.

There was evidence that at times patients with acute porphyria excrete very large quantities of P.B.G. and A.L.A., and that these very high levels of excretion may be maintained for only a relatively short time.

The excretion of these two metabolites and the changes in the nervous system are separate manifestations of a metabolic event or series of events.

Porphyric patients can present with symptoms which are a psychogenic reaction to environmental stresses, and the level of porphobilinogen in the urine does not assist in the diagnosis of the acute attack in such cases.

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Appendix

CLINICAL FEATURES OF PATIENTS

Case 1.—Female, aged 47. Abdominal symptoms, mental changes, and paralyses after barbiturates 6 years before. During investigation mental state normal; no pain but mild residual weakness of feet.

Case 2.—Female, aged 45. 8 years earlier abdominal symptoms, mental disturbance, and paralyses leaving residual claw-hands and partial foot-drop. Normal during investigation apart from brief periods of depression or anxiety.

Case 3.—Female, aged 37. Several attacks of abdominal symptoms, mental change, and weakness over 5 years. During first investigation no symptoms. During second investigation abdominal symptoms, fatigue, and depression but no physical abnormalities.

Case 4.—Male, aged 37. Severe attack of abdominal symptoms and pareses 6 years previously. Subsequent attacks of abdominal symptoms and depression. Three bouts of abdominal symptoms during investigation. First two coincided with peaks of porphobilinogen excretion.

Case 5.—Female, aged 57. Many attacks of abdominal symptoms with depression and hallucinations over 12 years. During investigation repeated abdominal symptoms and weakness with rapid recovery, some probably hysterical.

Case 6.—Male, aged 44. Attacks of abdominal symptoms for 15 years; severe paralysis with slow recovery 5 years before investigation. Residual bilateral claw-hand and foot-drop. Bouts of mild abdominal symptoms but mentally normal during investigation.

Case 7.—Female, aged 48. Confusion with mental defect and epilepsy since childhood. No other symptoms.

Case 8.—Female, aged 60. Attacks of abdominal symptoms with weakness of arms and paralysis of legs for 6 years. During investigation no symptoms of porphyria.

Case 9.—Male, aged 61. Attacks of abdominal symptoms, depression 14 years and 2 years earlier. No symptoms of porphyria during investigation.

Case 10.—Female, aged 23. Attack of abdominal symptoms 1 year before admission; further attack 2 days after admission. Mental condition constantly changing during period of study.

Case 11.—Male, aged 36. One attack of abdominal symptoms 3 years before. During investigation no physical or mental abnormality.

Case 12.—Male, aged 20. Attacks of severe abdominal symptoms for 1 year. Abdominal pain and apparently hysterical fits during investigation.

Case 13.—Female, aged 26. Attacks of abdominal symptoms for 10 years. Extensive muscular weakness with paralyses during and for two weeks before investigation.

Case 14.—Male, aged 22. Abdominal symptoms for 3 months. Mental state normal at first investigation. Readmitted with weakness. Severe mental symptoms but no abnormal neurological signs.

THE USES OF GLASSONA

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SPUN-GLASS and cellulose-acetate fibres, woven together and then knitted circularly (like stockinette), are supplied as bandages 3 yards long and 3 or 4 inches wide under the trade name of 'Glassona'. After immersion in either acetone, which is inflammable, or a mixture of methylene chloride 99·25% with industrial alcohol 0·75%, which is non-inflammable, the cellulose acetate dissolves. The bandage is then in a pliable state in which it can be moulded easily to a surface and one layer will bond to another. As the surplus acetone evaporates, the spun glass hardens. The material so produced has certain characteristics which make it very suitable for orthopædic splints. Plaster-of-paris has become so established as the material of splints that we tend to be complacent about its virtues; but we should not neglect to search for something better. Glassona is lighter and more durable than plaster-of-paris, impervious to water, and translucent to X rays. If distorted it regains its shape, so that a forearm or trunk splint can be sprung open after cutting down one side, removed, and then replaced without loss of fit or rigidity.

Disadvantages

Although available for seven years, glassona has not become widely used. It has one major disadvantage which discourages its routine use for splints—namely, that at room temperature rigid setting is not achieved for 3–4 hours. By means of a hot air drier the setting time of small splints can be accelerated to 15–30 minutes, but even this is too slow for the treatment of displaced fractures. The long setting time and the inconvenience of using a drying machine discourage the use of glassona whether manipulation is involved or not. Even with the aid of a drying machine it would not be safe to move a patient in a glassona hip-spica off the fracture table in less than an hour.

Fig. 1—Combined glassona-plaster spica.

The danger of using inflammable solvent in association with an electrical machine is obvious, but I do not believe that this has prevented more widespread use of glassona. The risk can be lessened by safe electrical equipment and by free ventilation to disperse the acetone vapour; ventilation is necessary, too, to prevent acetone sickness. With these precautions the routine use of glassona is no more fraught with danger than many common medical procedures—e.g., the use of inflammable anæsthetic agents.

Combined Glassona-plaster Splints

The reason why glassona has not become popular as a splinting material in routine orthopædic work is due more to its long setting time than any other consideration. I have tried to counteract this disadvantage by combining glassona with plaster-of-paris temporarily or permanently in the making of splints, and in seven years' use I have found this to be of great advantage and without undue risk.

My method is to use a light cast of plaster to stabilise the part to be splinted. The glassona fraction of the splint

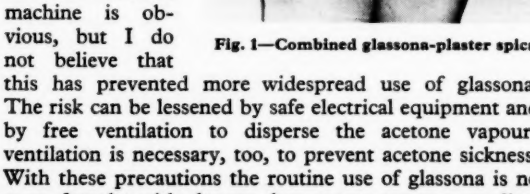

Fig. 2—Outer plaster shell being removed to leave a glassona splint.

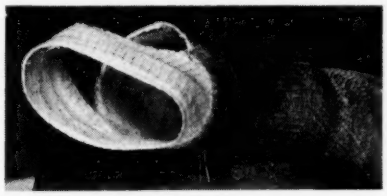

Fig. 3—To show the rigidity of a glassona splint.

is applied over or under the plaster, and allowed to dry naturally. The end-product is a splint of combined glassona-plaster or a splint of glassona only. The patient is instructed to treat the cast gently for three hours; afterwards it will be more durable than any cast made of an equal number of plaster bandages.

The combined glassona-plaster splint has the glassona as an outer waterproof layer. A spinal jacket of average adult size can be made of six 8-inch plaster bandages and two or three 4-inch glassona bandages. At a later stage in the treatment, if indicated (e.g., to measure for a corset), such a spinal jacket can be cut down one side, sprung open, and removed. It can be reapplied and fixed with a crepe bandage or ' Elastoplast ' binding. An average-sized hip-spica can be made from a plaster base of ten 8-inch bandages and a covering layer of three or four 4-inch glassona bandages (fig. 1). (The successive circles of glassona overlap by about a third of the width.) Such a spica is much lighter and more durable than any plaster spica of equal strength, and the waterproof covering is an obvious advantage, particularly for children. Penetration by X rays is better through these combined splints than through plaster splints.

Glassona Splints

Sometimes it is useful and practical to remove the plaster fraction of a combined splint once the plaster and glassona have become rigid. The glassona then no longer depends on the plaster fraction for its rigidity, strength, or durability. If the plaster fraction is removed the splint becomes lighter and can be immersed in water without softening. By cutting down one side the splint is converted into a light waterproof removable splint; such a forearm splint is particularly useful for treating acute tenosynovitis about the wrist. Spinal supports and knee cylinders, too, can be made after this fashion.

When it is intended to remove the plaster fraction of a combined splint the glassona fraction is applied first over a layer of stockinette. A further layer of stockinette or wool is placed over the glassona, and over this the plaster fraction is applied. The part is held immobile until the plaster has set. Next day the outer plaster shell is removed together with the barrier layer of wool or stockinette (fig. 2). A rigid splint of glassona is thus achieved with no inconvenience from the long setting time (fig. 3).

In none of these procedures does glassona come into direct contact with the skin, and so skin irritation is avoided. The operator's hands should be protected by gloves.

TRIPLOID CELL CULTURES FROM A MACERATED FŒTUS

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ALTHOUGH the first accurate observations on normal human chromosomes (Tjio and Levan 1956) were made with cell cultures taken from fœtal tissues, the opportunities for investigating the chromosomes in cases of natural abortion have not so far been greatly exploited. We here describe the results of culturing cells from fœtal remnants in a case of missed abortion.

The *patient*, whose offspring was studied, is a healthy woman aged 44. She had one previous pregnancy at the age of 41, which resulted in a normal boy. The second pregnancy began during the third week of August, 1960 (last menstrual period, Aug. 8). The xenopus test was positive on a specimen taken on Oct. 3. About a week later a very slight bloodstained discharge was noted. Eight weeks afterwards (Nov. 30) the uterus was found to be definitely too small to be compatible with a normal pregnancy of twelve weeks' duration or more,

Triploid cell from yolk sac, culture C, with chromosome analysis.

and missed abortion was suspected. Curettage was performed on Jan. 2, 1961. A routine pathological report, by Dr. N. F. C. Gowing, indicated the presence of living and dead placenta, showing normal vascularisation. The patient's recovery was uneventful.

A sterile *specimen* from the uterine contents, including the supposedly fœtal material (in glucose saline) was kindly provided by Mr. Clifford Simmons. The specimen consisted of an amorphous spongy mass, about 15 cc. in volume. When spread out, it was found to contain some completely disorganised tissues which appeared to be of fœtal origin but which were inseparable from the main mass of degenerated placenta. There was evidence of calcification. In the centre was a yellowish narrow firm tubular structure, not freely detachable, which was thought to be fœtal gut. A small bladder with a delicate transparent wall, attached to a short stalk and full of clear fluid, was believed to be the yolk sac.

Two *cultures*, A and B, were taken from the gut area, and one, C, from the yolk-sac wall. The explants, each about 4 c.mm. in volume, were divided into smaller pieces for culture. The cultures were set up on Jan. 4, the procedure closely following that described by Harnden (1960). Growth was, at first, rapid in cultures B and C; culture A grew more slowly. Slides for cytological examination were obtained on Jan. 23. Good preparations were difficult to obtain, especially in B and C, because of the tendency of cells to aggregate in clumps in a manner characteristic of cultured epithelial cells, and mitoses were not plentiful. Later the cultures continued to grow, but very slowly.

Investigation of the *karyotype* in A showed that all cells contained 46 chromosomes, as in a normal female. Cultures B and C, however, revealed a triploid condition, with 69 chromosomes in nearly all unbroken cells, though a few were hexaploid, with 138 chromosomes. Analysis of the triploid cells clearly revealed 7 small acrocentric chromosomes, one of which could reasonably be supposed to be a Y. As the figure shows, there can be little doubt about the interpretation of these cells as true examples of a triploid condition in which one set of 23 chromosomes was derived from a sperm, and two sets from an ovum. The fact that in each trio (and especially the larger ones) two chromosomes seem to be morphologically very similar, supports this view. Probably the cause of the triploidy was fertilisation of an unreduced ovum which had undergone the first, but not the second, meiotic division.

Two cytological investigations were made to throw light on the origin of these karotypes. The cells in a culture of the patient's peripheral blood, made by Miss Ruth Marshall, contained a normal female chromosome complement; so the cells which grew in culture A could have been endometrial in origin. To test the possibility that fœtal membranes might normally be triploid, a culture was taken from the amniotic sac of a normal male fœtus at four months. This was found to be diploid.

Triploidy in mice, rabbits, and rats is known to occur spontaneously (Austin 1960); it can also be produced artificially in mice by temperature shock, or by treating ova with colchicine before fertilisation (Beatty 1951). Such embryos rarely complete their development. Mosaic or chimæric animals—heteroploids with both triploid and diploid cells—have also been found. In man there is the example of a malformed 2-year-old boy reported recently (Böök and Santesson 1960, Böök 1961). Here, 84% of the cells from skin biopsy, and 49% of cells cultured from connective tissue, but none of the cells in peripheral blood or bone-marrow, showed a triploid condition almost exactly like that shown in the figure. The normal cells were diploid male. It is possible that the fœtus we studied may also have been heteroploid, though this seems unlikely because none of the cultures was mosaic.

Two points arise from this investigation. Triploidy following fertilisation of unreduced ova might cause abortion more often than has been formerly supposed. Successful culturing of material from a macerated fœtus, nearly two months after it had ceased to develop, is unexpected but encouraging for future studies of spontaneous abortion.

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DETERMINATION OF SERUM-THYROGLOBULIN BY A HÆMAGGLUTINATION-INHIBITION TEST

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IT has been shown by several workers (Roitt et al. 1958, Witebsky et al. 1958) that the thyroid autoantibody in human serum, which can be demonstrated by precipitation and by Boyden's hæmagglutination reaction, is an antibody to thyroglobulin. The antibody was first discovered in Hashimoto's disease (Roitt et al. 1956), and later was found in other thyroid diseases (Paine et al. 1957, Roitt and Doniach 1958, 1960). It can be found occasionally even in normal people and patients without thyroid disease (Hackett et al. 1960).

Thus the demonstration of thyroglobulin in serum has become important.

Lerman (1940) demonstrated thyroglobulin by precipitation with a thyroglobulin antiserum prepared from rabbits. No thyroglobulin could be found in the serum of normal people or of patients with thyrotoxicosis or myxœdema. But immediately after operations on the thyroid gland thyroglobulin could often be found in blood from a thyroid vein, and in exceptional cases in blood from a cubital vein.

Later Robbins (1954) and Robbins et al. (1954), by "salting out" and by ultracentrifugation, found thyroglobulin in the serum of patients after therapeutic doses of radioiodine (^{131}I). Stemmermann (1956) found an increase in the α_2-globulin in the serum of 4 patients with subacute thyroiditis. This, he considered, was due to extruded colloid from the thyroid gland. Finally, Owen and McConahey (1956) demonstrated a thyroglobulin-like protein in the serum of the majority of 38 patients with Hashimoto's disease.

If thyroid operations cause a leakage of thyroglobulin, the situation closely resembles that in animal experiments on immunisation by thyroglobulin (Shepherd et al. 1960, Terplan et al. 1960). We have therefore examined a series of patients undergoing thyroid surgery to find out whether thyroglobulin or thyroglobulin antibody is demonstrable in the serum immediately or shortly after operation.

TABLE I—DETERMINATIONS OF THYROGLOBULIN BY THE HÆMAGGLUTINATION-INHIBITION TEST

—	Dilutions of test serum containing thyroglobulin antibody (0·1 ml. in each cup)						
	1/30	1/150	1/300	1/600	1/1200	1/2400	1/4800
Patients' serum:							
Before operation ..	+	+	+	+	+	±	−
After operation:							
1st day	+	+	−	−	−	−	−
3rd ,, ...	+	+	±	−	−	−	−
6th ,, ...	+	+	+	+	+	−	−
Normal serum + thyroglobulin:							
20 µg. per ml. ..	±	−	−	−	−	−	−
10 ,, ..	+	−	−	−	−	−	−
5 ,, ..	+	±	−	−	−	−	−
2 ,, ..	+	+	±	−	−	−	−
1 ,, ..	+	+	+	−	−	−	−
0·5 ,, ..	+	+	+	±	−	−	−
0·2 ,, ..	+	+	+	+	±	−	−
0·1 ,, ..	+	+	+	+	+	−	−
0 ,, ..	+	+	+	+	+	+	−

The example shows moderate leakage of thyroglobulin in a 58-year-old woman after partial thyroidectomy.

Methods

Thyroglobulin was prepared by the method of Derrien et al. (1948). Thyroglobulin antibody was demonstrated by Boyden's hæmagglutination technique (1951), which was performed mainly as described by Roitt and Doniach (1958). We used sheep erythrocytes which, after coating with thyroglobulin, were treated with formalin by the method of Fulthorpe (1957).

Thyroglobulin was demonstrated by a hæmagglutination-inhibition technique. The determinations were performed in 'Perspex' agglutination trays. After inactivation (at 56°C for thirty minutes) and absorption with washed sheep erythrocytes, a series of dilutions was prepared of a serum containing thyroglobulin antibody, and with a known titre in the hæmagglutination reaction. The titre should not be below 2000–3000.

TABLE II—SERUM-THYROGLOBULIN IN 29 PATIENTS BEFORE AND AFTER THYROID OPERATIONS, COMPARED WITH THE RESULTS OF THYROGLOBULIN-ANTIBODY DETERMINATIONS 1 MONTH AFTER OPERATION

Case no.	Sex	Age (yr.)	Clinical condition	Approx. serum-thyroglobulin content (µg. per ml.)				Thyroglobulin antibody 1 month after operation (hæmagglutination titre)
				Before operation	After operation			
					2nd day	6th day	1 month	
1	F	16	Euthyroid	0	>10	10	0	0
2	F	22	,,	0	2	0·2	0	0
3	F	22	,,	0	≧10	5	0	0
4	F	25	,,	0	10	0	0	0
5	F	27	,,	0·5	≧10	2	0	0
6	F	34	,,	0	0	0	0	0
7	F	41	,,	0	0	0	0	0
8	F	46	,,	0	1–2	0·2	0	0
9	F	46	,,	0	1	0	0	0
10	F	48	,,	0	0	0	0	0
11	F	49	,,	0	2	N.E.	0	0
12	F	50	,,	1	2	N.E.	0	0
13	F	51	,,	0	10	N.E.	0	0
14	F	52	,,	0	2	0	0	0
15	F	53	,,	0	1–2	0	0	0
16	F	56	,,	1	1	0	0	0
17	F	64	,,	0	10	0·2	0	0
18	F	67	,,	0	0·2	N.E.	0	0
19	F	24	Hyperthyroid	0	1	0	0	0
20	F	28	,,	0	2	0·5	0	5
21	F	35	,,	0	>10	N.E.	0	0
22	F	38	,,	0	10	N.E.	0	0
23	F	39	,,	0	10	0	1	0
24	F	46	,,	0	10	1	0	0
25	F	53	,,	0	1–2	0	0	0
26	F	56	,,	0	2	N.E.	0	0
27	M	57	,,	0	0	0	0	0
28	F	63	,,	1	1	N.E.	0	0
29	F	65	,,	0	0	N.E.	0	0
Ratio of patients with thyroglobulin, or thyroglobulin antibody, to the no. of cases studied			Euthyroid	3/18	15/18	6/14	0/18	0/18
			Hyperthyroid	1/11	9/11	2/6	1/11	1/11
			Total series	4/29	24/29	8/20	1/29	1/29

A hæmagglutination inhibition corresponding to a serum-thyroglobulin content of 0·1 µg. per ml. was considered doubtful, and therefore excluded; N.E. signifies not examined.

For greater sensitivity, the highest dilutions should preferably be doubling dilutions. The highest dilution must give a negative reaction. 0·1 ml. of these serum dilutions was deposited by means of a dropping pipette (3 drops = 0·1 ml.) in each cup of the trays in "vertical" rows. To each of the dilutions was then added 0·1 ml. of the serum which was to be examined for thyroglobulin (i.e., to the "horizontal" rows in the trays). These specimens had also been inactivated and absorbed with sheep erythrocytes before use. The trays were then covered with lids, and placed in an incubator at 37° C for four hours, after which time 0·1 ml. of a 1% suspension of thyroglobulin-coated and formalin-treated sheep erythrocytes was added to each cup. The trays were left overnight at room temperature, and read next morning. For each serum was included a control to which erythrocytes treated with tannin and formalin had been added.

In each determination, standard serial dilutions of the serum containing thyroglobulin antibody were prepared, in which the patients' serum was replaced by normal serum to which known amounts (0-20 µg. per ml.) of a purified thyroglobulin fraction had been added. By comparing the experimental series with these standards one can obtain a certain quantitative measure of the amount of thyroglobulin (see table I).

TABLE III—THYROGLOBULIN-ANTIBODY DETERMINATIONS IN 7 PATIENTS WITH THYROGLOBULIN ANTIBODY BEFORE OPERATION

Case no.	Sex	Age (yr.)	Clinical condition	Thyroglobulin antibody (hæmagglutination titre)			
				Before operation	After operation		
					2nd day	6th day	1 month
1	F	61	Euthyroid	5	0	25	0
2	F	13	Hyperthyroid	125	25	N.E.	125
3	F	14	,,	125	125	125	125
4	F	30	,,	25	0	125	25
5	F	45	,,	125	0	N.E.	125
6	F	60	,,	125	25	N.E.	25
7	F	70	,,	5	0	5	5

N.E. signifies not examined.

The Patients

There were 35 women and 1 man. Partial thyroidectomy had been performed in 30, hemithyroidectomy in 3, and enucleation of adenoma in 3. The thyroglobulin and thyroglobulin antibody were determined before operation, and afterwards on the second day, the sixth day (only in 24 patients), and a month later. 17 of the patients were hyperthyroid, and 19 were euthyroid (non-toxic goitre, non-toxic adenoma).

Results

Among 132 normal subjects (blood-donors), only 1 revealed traces of thyroglobulin in the serum (about 0·2 µg. per ml.).

Before operation no thyroglobulin antibody could be demonstrated in 29 (18 euthyroid and 11 hyperthyroid) of the 36 patients. The serum-thyroglobulin determinations in these patients are given in table II. In 4 cases, small amounts of thyroglobulin were found (1 µg. per ml., or less). On the second postoperative day, thyroglobulin was present in the serum in 24 (83%) of the patients in this group (in 10 of these the inhibition corresponded to 10 µg. per ml. or more), and thyroglobulin could still be demonstrated in 8 of 20 samples taken on the sixth day. A month after operation only 1 patient (case 23) had thyroglobulin in the serum (the hæmagglutination-inhibition reaction had been negative on the sixth day after operation, and later). A patient (case 20) in whom thyroglobulin was still found on the sixth day showed traces of thyroglobulin antibody a month after operation, but the hæmagglutination test was positive only at the lowest serum dilution (1/5).

7 patients (1 euthyroid and 6 hyperthyroid) had thyroglobulin antibody in low titres in the serum before operation. Their hæmagglutination titres are given in table III. In 6 of them the titre fell transiently after operation; thus on the second day after operation, no antibody could be demonstrated in 4 of the patients, whereas thyroglobulin was demonstrated in 2 (cases 5 and 7). In the samples taken on the sixth day the antibody was again present. The transient fall in the amount of antibody may be explained as a result of an in-vivo antigen-antibody reaction between extruded thyroglobulin and thyroglobulin antibody. On the sixth day, 2 patients showed increases in the hæmagglutination titre to values higher than before operation, but otherwise there were no signs of stimulation of antibody production due to antigen leakage.

Determinations of complement-fixing antibody (as described by Roitt and Doniach 1958) were also performed. In 8 patients (1 euthyroid and 7 hyperthyroid, including cases 2, 3, and 7 in table III) complement-fixing antibody was demonstrated before operation. None of these patients showed a transient fall in the amount of complement-fixing antibody.

Discussion

The results confirm Lerman's (1940) observation that thyroglobulin may leak into the circulation after operation upon the thyroid gland. By his precipitation technique, Lerman could only occasionally demonstrate thyroglobulin in blood withdrawn from an arm vein. The great sensitivity of the hæmagglutination reaction made it possible to reveal thyroglobulin in the circulation in most of the patients in the present series. Lerman expressed the view that the thyroglobulin very rapidly disappeared from the bloodstream, but I could not confirm this. It seems as if thyroglobulin leaks continuously during the first few days after operation, since several of the patients from whom successive samples were taken postoperatively only reached their maximum serum-thyroglobulin content after two or three days.

The transient postoperative fall in the hæmagglutination titre in patients who had thyroglobulin antibody in the serum before operation can apparently be explained only by an antigen-antibody reaction in vivo. (There was no fall in the hæmagglutination titre in a patient who underwent an intestinal operation.) The fact that autoantibodies are considered to be the most specific form of antibodies (Shulman and Witebsky 1960) strongly suggests that it is the true antigen which is present in the serum after operation. In addition, the fall in titre shows that free thyroglobulin must have been present in the thyroid glands of these patients. This has previously been demonstrated in vitro (Witebsky et al. 1958). Unfortunately, the amount of free thyroglobulin was not determined in the thyroid tissue removed from our patients, but further studies are in progress.

Although, as shown, thyroglobulin leaked into the circulation in most of the patients in relation to operation, only 1 patient had evidence of weak autoimmunisation after a month. This is not surprising, and it agrees with the findings in animal experiments (Terplan et al. 1960, Shepherd et al. 1960). Thus, simple contact between thyroglobulin and the antibody-producing cells does not seem to be enough to provoke the formation of thyroglobulin antibody.

Summary

By a hæmagglutination-inhibition technique it was shown that thyroid surgery was followed by leakage of thyroglobulin into the circulation in 24 of 29 patients who had no thyroglobulin antibody in their serum before operation. Only 1 of these patients had traces of thyroglobulin antibody a month after operation.

In 6 of 7 patients with thyroglobulin antibody in the serum initially, thyroid surgery was followed by a transient fall in the hæmagglutination titre. This fall may be the result of an in-vivo antigen-antibody reaction.

In 8 patients with complement-fixing thyroid autoantibody in the serum no transient fall in the amount of antibody could be demonstrated after operation.

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RECONSTITUTION OF FROZEN RED CELLS

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FROZEN glycerol-treated red cells have, since Chaplin and Mollison's report (1953), found a place in almost all blood-grouping laboratories. Indeed, some of the progress made in this field is due to rare and very rare cells having thus become available at any time as test cells. That frozen cells have not found still more universal application is possibly because their reconstitution according to the original method (the " glycerol method ") is somewhat laborious, and because, once reconstituted, the cells are " sticky ". Many workers also complain that they often give positive direct Coombs tests (without being " coated "), thus being useless as reagents in the investigation of antibodies which manifest themselves mainly in this test. In a busy laboratory it is often difficult for the technicians to find time for the many washings required, and to spare the centrifuges for long enough. Sloviter (1951) and Mollison and Sloviter (1951) mentioned a method of reconstituting frozen red cells by dialysing them against decreasing concentrations of glycerol. But the method was never used on a large scale, because it seemed too cumbersome, it took too long, and the results did not seem to be better than with the glycerol method. It seemed that if one could avoid these shortcomings, though admittedly not grave, frozen cells might become still more acceptable for general use. I therefore devised a different method, and as the results seemed to be very good I asked other interested workers to try it.

Method

According to the volume of cells needed, a length of ' Visking ' dialising tubing * is cut off. 5 cm. is ample for volumes of, say, 0·2 ml. of cells; 20 cm. will comfortably accommodate up to

*Tubing of small ($^3/_{32}$ in.) diameter has proved suitable; this may be had from Hudes Merchandising Corporation, Ltd., 52, Gloucester Place, London, W.1.

5 ml. of cells. The cells are thawed, and the amount needed for the day's work is removed from the container with a dry long-stemmed pasteur pipette. This is introduced into the visking tubing, and the cells are delivered into it. The pipette is then withdrawn, and the two ends of the tubing with the cells inside are brought together, folded over, and tightly closed by either a Spencer-Wells forceps or a paper-clip. At this stage it is important that nothing should enter the lumen of the tubing. If more than one sample of cells is being prepared, I find it convenient to tie an identifying label to the paper-clip or the tubing itself. The whole length of tubing is then immersed in a vessel, which has previously been filled with physiological saline, and left at room temperature. Beakers of about 200 ml. capacity will comfortably accommodate four or five cell samples in their tubings. No agitation is necessary. As for the time during which the tubing should stay immersed, 15 minutes proved to be just long enough, but so short a time is not advisable, and the results are better after 30 minutes and better still after 1–2 hours. I have also left the tubing in the saline overnight without detriment to the end result.

When the tubing is eventually removed from the saline bath, the forceps or paper-clips are removed. A pasteur pipette filled with saline is introduced into one end, and the other end is put into a previously labelled test-tube. For amounts up to 1 ml., test-tubes of 7×1 cm. are suitable; for larger quantities, "universal containers" can be used. The saline is next discharged into the visking tubing to expel the cells into the container, which is then filled up with saline and spun down. I have found that spinning for 30–60 seconds at 3000 r.p.m. is adequate. The supernatant, which may show some slight hæmolysis, is discarded. The deposited cells are then resuspended in fresh saline, and spun down once more; after the supernatant has again been removed, the cells are ready for use.

Comment

The initial hæmolysis depends somewhat on the length of immersion in saline; there is more hæmolysis after 15 minutes, and much less after, say, 1–2 hours. With this method the cells showed less hæmolysis than with the glycerol method. The new method also has the advantages that much less time is needed to reconstitute the cells, and that the cells are not sticky and can easily be suspended. The cell suspension is smooth even after the first spinning. None of the many cell samples tested has given a positive Coombs test, even with very potent anti-human-globulin sera. The cells seem to be less damaged than when reconstituted by the glycerol method, because they all stand modification by the usual enzymes (trypsin, papain, and ficin) very well. In my previous experience, when frozen cells were reconstituted, they could not be kept overnight without much hæmolysis. On the other hand, cells reconstituted by the new method have kept well for 72 hours and showed only traces of hæmolysis. With this method the antigens seem to be well preserved. The same antiserum titrated against cells reconstituted by both methods gave, if anything, slightly higher scores with the cells treated by the new method; even antigens, which experience has shown do not keep well, could be demonstrated (e.g., the P antigen). A few experiments were performed to see whether cells (kept at $-25°C$ for at least a year) which had been papainised and then frozen were usable; they gave slightly higher scores when compared with cells reconstituted by the glycerol method. They gave also a sharper end-point (Miss D. A. Battey and Dr. H. M. Halley, unpublished observations).

Lastly, cells coated by antibody were also reconstituted by the new method. Unfortunately cells stored for long periods were not available, but cells which had been stored for a short time gave an equally strongly positive Coombs test after reconstitution as before they were frozen. If long storage does not affect the strength of the Coombs test (cells reconstituted by the glycerol method were not always satisfactory), such cells could be used as readily available control cells for the Coombs reagent, and time could be saved in preparing "controls" every day. These cells would, of course, control the Coombs reagent only; "controls" would still have to be prepared for the washing.

Whether this method will prove feasible for reconstituting large volumes of blood for transfusion purposes is not yet clear. Further work will be necessary with particular regard to the problems of sterility.

Summary

A method is described for reconstituting frozen glycerolised cells which seems to be convenient, easy, and quick, and which produces cells suitable for the usual serological investigations.

Dr. R. R. Race, Dr. Ruth Sanger, and Miss P. Tippett were good enough to test the method, and I am very grateful for their encouragement and kindness.

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Preliminary Communication

PITUITARY RESPONSE TO PYROGEN IN CUSHING'S SYNDROME

Cushing's syndrome with adrenal hyperplasia may result from increased secretion of corticotrophin.[1–4] Is this increased secretion itself due to an enhanced response to stimulation by the pituitary? This was tested in three patients with Cushing's syndrome, by comparing the pituitary response to stimulation with bacterial pyrogen with the response to a standard infusion of corticotrophin.

METHODS

The pyrogen (Organon), a bacterial polysaccharide, was injected intravenously in a dose of 0·005 μg. per kg. body-weight. Bacterial pyrogen stimulates pituitary secretion of

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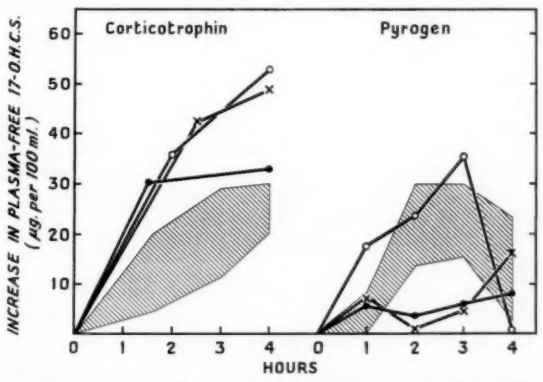

Response to corticotrophin and pyrogen in three cases of Cushing's syndrome.

The shaded areas contain the range of response in five subjects convalescent from various non-endocrine diseases.

FINDINGS IN THREE CASES OF CUSHING'S SYNDROME

Case No.	Age (yr.)	Sex	Urinary 17-O.H.C.S. (mg. per day)				Plasma-free 17-O.H.C.S. (μg. per 100 ml.)	
			Before corticotrophin		After corticotrophin		Before suppression	During suppression
			Norymberski	Porter-Silber	Norymberski	Porter-Silber		
1	16	F	..	..	..	..	24·0	2·0
2	34	F	..	15·7	..	85·0	23·8	8·0
3	33	F	30·4	..	84·4	..	36·2	25·0

corticotrophin.[5–7] In normal individuals the maximum increase in plasma-free 17-hydroxycorticosteroids (17-O.H.C.S.) concentration occurs two to four hours after injection of the pyrogen, and is on average 75% of the increase in the same subjects during a four-hour intravenous infusion containing 25 I.U. corticotrophin.[8]

RESULTS AND DISCUSSION

Diagnostic

All three patients had clinical features of Cushing's syndrome; and their plasma-17-O.H.C.S. concentrations, measured by the method of Peterson et al.,[9] on several occasions preoperatively were at the upper limit of normal (26 μg. per 100 ml.) or above normal, the means of several plasma samples from each patient being 22, 23, and 24 μg. per 100 ml. plasma. The response to corticotrophin was greater than normal in all three (see figure). In two of the patients, the urinary 17-O.H.C.S. output was increased, and the response to corticotrophin gel (Armour), in a dose of 60 I.U. twice daily for three days, was enhanced (see table). Adrenal suppression was seen in two patients after dexamethasone (1·5 mg. six-hourly), but was only slight in case 3 who was given triamcinalone (8 mg. six-hourly). Triamcinalone has only about 3% of the chromogenicity of cortisol with the Porter-Silber reagent,[10] and does not contribute appreciably to the plasma-free 17-O.H.C.S. concentration. There was no diurnal variation in plasma-17-O.H.C.S. concentrations in the two patients in whom it was measured. Bilateral adrenal hyperplasia was confirmed at laparotomy, and bilateral adrenalectomy was performed in all three patients. The adrenals were examined histologically in cases 1 and 2 and showed bilateral adrenal hyperplasia.

Response to Pyrogen and Corticotrophin

The response to pyrogen is shown in the accompanying figure. In two of the patients (crosses and closed circles in figure), despite the supranormal response to corticotrophin the response to pyrogen was less than normal. The poor response to pyrogen does not indicate that the pituitary was already secreting corticotrophin at its maximal rate, since in all three patients the plasma-free 17-O.H.C.S. concentrations before pyrogen were only at the upper limit of normal. In the third patient (see figure, open circles) the dose of pyrogen given was inadvertently 20% greater than that calculated from the body-weight. Despite this increased dose the response was only little above the response to the smaller dose in normal subjects. More important, it was appreciably less than the response to corticotrophin.

Apparently, therefore, the increased concentration of circulating corticotrophin which is found in some patients with Cushing's syndrome is not likely to be the result of enhanced pituitary response to stimulation.

We are grateful to Prof. Harold Scarborough for his help and encouragement; to the Medical Research Council for a grant for technical assistance; and to Dr. W. J. Tindall, of Organon Laboratories, for the bacterial pyrogen.

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Medical Societies

HEBERDEN SOCIETY

A JOINT meeting of the Ligue Française contre le Rhumatisme and the Heberden Society was held in Paris on May 27 and 28.

Hemiplegia and Arthritis

Dr. MALCOLM THOMPSON (Newcastle upon Tyne) and Prof. E. G. L. BYWATERS (London) described 4 cases indicating that hemiplegia protected against rheumatoid arthritis on the paralysed side.

Distribution of Gold in Body

Dr. J. S. LAWRENCE (Manchester) described the distribution of gold in the body after intramuscular injection of 10 mg. doses of aurothiomalate labelled with ^{198}Au in 10 patients with rheumatoid arthritis. Scanning of seventy joints with a scintillation counter showed that painful joints gave higher counts—up to two and a half times as high as symptomless joints. Pronounced concentration of gold was noted in the fibrin clot from a joint and in articular cartilage. Gold compounds might have a local action on inflamed tissues due to inhibition of enzymes concerned in the inflammatory process.

Osteoarthritis of Hip

Dr. J. CORDIER, Dr. H. GARNER, and Dr. M. DARCY (Paris) described the results of an operation for osteoarthritis of the hip in which the principle was section of the periarticular muscles in an attempt to overcome the painful muscular hypertonia in the region of the affected joint. More than a hundred patients had been operated on, and 54 had been followed up for at least six months. Of these, 23 had excellent results as regards pain and function, and 21 had good results.

Gout

Dr. G. D. KERSLEY (Bath) described experience with four uricosuric agents—probenecid, ethebenecid, sulphinpyrazone, and zoxazolamine—in 50 cases of gout followed over the past three years. Sulphinpyrazone 800 mg. daily was found to be the most potent uricosuric agent. Ethebenecid was found to be as effective as, and less toxic than, probenecid; and zoxazolamine was of similar potency. Aspirin inhibited the uricosuric action of all these agents, but paracetamol did not do so. In the first few weeks of uricosuric therapy symptoms tended to be exacerbated; so it was wise to cover this period with colchicine. It was important to continue uricosuric therapy even after the serum-uric-acid level had reverted to normal.

Osteotomy in Hip-joint Dysplasia

Prof. MERLE d'AUBIGNÉ, Dr. M. POSTEL, and Dr. J. M. VAILIANT (Paris) described the results of osteotomy in hip-joint dysplasia, with and without secondary osteoarthritis. 200 patients had been operated on over the past seven years and 100 had had at least one year follow-up. Of some 35 cases, with partial subluxation of the hip, operated on before the onset of arthritis, 86% had no pain at follow-up, practically all had retained the preoperative range of movement, and 70% walked normally. Where osteoarthritis was present (79 cases) 85% now had painless hips, but in 7 pain had increased requiring further surgery. Radiological follow-up showed improvement in the state of the osteoarthritis in 19, no change in 50, and slight aggravation in 10. They concluded that osteotomy of the neck of the femur had given useful results in hip-joint dysplasia, both before and after onset of osteoarthritis.

Methandrostenolone with Corticosteroid Therapy

Dr. H. COLENBRANDER (Leiden) and Dr. BARBARA ANSELL (Taplow) had sought to establish whether administration of methandrostenolone, an anabolic steroid, to patients on maintenance corticosteroid therapy for various rheumatic diseases would prevent or ameliorate spinal osteoporosis. In all patients over the age of 16 there was no difference between the control and treated groups. In juveniles the results were less clear-cut. Side-effects were common; and it was concluded that this was not a practical means of controlling steroid osteoporosis.

Reviews of Books

Management of Hypertensive Diseases

JOSEPH C. EDWARDS, A.B., M.D., F.A.C.P., F.A.C.C., assistant professor of clinical medicine, Washington University School of Medicine, St. Louis, Mo. St. Louis: C. V. Mosby. London: Henry Kimpton. 1960. Pp. 420. 112*s*. 6*d*.

ONE of the doctor's dilemmas is the potential seriousness of hypertension and the potential efficacy of modern treatment, yet we lack so far a really satisfactory drug for lowering blood-pressure. Another difficulty is the number of relative rarities to be excluded before treatment is begun, and the need, therefore, for hospital assessment. For the physician who must be familiar with all aspects of the problem, this book covers the ground. It is beautifully produced, a pleasure to have, and despite the forbidding price, strongly to be recommended. Clearly written by a clinician experienced in the problems of assessment and management of hypertension, it is remarkably up to date, there being, for example, a full account of guanethidine, and the references go well into 1960.

The author says he has written for "the busy physician in practice who wants the latest information". In this country the book may not appeal to practitioners who do not have the responsibility or facilities for investigation and cannot be familiar with details of hospital techniques. It should, however, be of great value to most physicians who have full responsibility for assessment and treatment but do not work in large centres where all facilities are available and where there are ample opportunities for discussion and ready access to libraries.

There is much to praise and little to criticise. The author has been to much pains over the references and the fact that over 1600 are quoted is in itself of great value to workers in this subject. There is little attempt, however, at appraisal, and the reader must assume the author's agreement with the single statement quoted or accept that there are conflicting opinions. A personal opinion would have been valuable.

It is perhaps unnecessary to include in a book on hypertension such details as a two-page comparative chart about the various preparations of digitalis and details of other measures which are common to many cardiovascular disorders, and there might be more emphasis on the importance of atherosclerosis associated with hypertension. Much sensible advice is included in the well-selected case-histories which illustrate many problems and how to deal with them.

Recent Advances in Human Nutrition

Editor: J. F. BROCK, D.M., F.R.C.P., professor of medicine, University of Cape Town. London: J. & A. Churchill. 1961. Pp. 454. 50*s*.

THE first third of this book has been the direct responsibility of Professor Brock, and the remaining sixteen articles are the work of men who have devoted themselves to more specialised aspects of the subject—such as the dietary fats, nutrition in the French and Spanish-Portuguese speaking countries, and the interactions between nutrition and the endocrine glands, infection, and the skeleton. The result is a happy marriage of the general and the particular, and the book illustrates how successfully our present knowledge has been, and could be further, applied to world problems; but at the same time it emphasises how defective knowledge is when it comes to some of the basic principles, and consequently how hesitating our advice must be on many points. The book, in short, deals with the nutritional problems of all sorts and conditions of man.

Professor Brock and a number of his co-authors work in South Africa or in tropical countries and their interests naturally centre on the state of nutrition in these so-called backward parts of the world. In spite of this, kwashiorkor and protein malnutrition have not been allowed to dominate the picture, although they have received their fair measure of attention and have been used freely to illustrate particular points. The difficulties facing the family doctor in advising his intelligent patients about fat, vitamins, and requirements in general have not been forgotten. The solutions, however, are not blazoned on the title page, for these problems have not been solved—the "state of play" at the present moment is all that anyone can be expected to give.

Professor Brock has shown his wisdom in the parts of the book he has written himself and also in his choice of authors for the remaining parts. The book may be commended to all those interested in the nutrition of the world or indeed in that of their families, whether they live in a prosperous country where many people die of coronary disease, or in less favoured country where 50% of those that are born never grow up to get the chance.

Agents of Cultural Advance

Sir AUBREY LEWIS, M.D., F.R.C.P. L. T. Hobhouse Memorial Trust Lecture, London: Oxford University Press. 1961. Pp. 29. 5*s*.

Professor Lewis, the first psychiatrist to deliver the L. T. Hobhouse Memorial Trust Lecture, has done so in a spirit of humility, knowing that Hobhouse disapproved of psychiatrists who tended to claim too much. Hobhouse once said: "People cannot even make discoveries—quite real and genuine discoveries—in morbid psychology without attempting to annex the whole realm of mind in their name."

Lewis discusses the criteria that have been laid down for cultural advance: it should satisfy the healthy, psychological, and physical needs of the individuals composing the society more than did the culture it grew out of or replaced; it should promote the closer integration and the stability of the society; and it should favour collective survival. Most of his lecture is devoted to the influence of exceptional individuals on cultural advance. The distinguishing characters of these people have not been fully understood, despite psychological and social studies, and their feats compel reflection about the relationship between abnormality that consists in outstanding achievement and abnormality that we classify as mental disorder. Furthermore, notable work may be looked on as substitute gratification and the genesis of certain features in it can be retraced like symptoms. But this tells us nothing about the distinctive quality that makes it valuable nor about the conditions of its realisation. The mastery of the creative process eludes psychological analysis and the value of outstanding work cannot be raised or lessened by considering the medical condition of the man or woman who created it.

Professor Lewis suggests that we commonly underestimate the range of intellectual power of which human beings are capable. We concentrate too much on its minus variants—on disorder and defect—leaving those with maximum potentiality

to develop this as luck and the educational system may determine. We do not know how to develop the potentialities of either our very gifted children or of those less gifted. We have not enough respect for what is statistically abnormal, yet " the departure from the normal may be most rare and wonderful ".

Advances in Virus Research

Vol. 7. Editors: KENNETH M. SMITH, MAX A. LAUFFER. New York and London: Academic Press. 1960. Pp. 397. 80*s*.

Advances in Virus Research has established itself as essential reading for all virologists, and this volume maintains the high standard, though increasing specialisation has put most of these review articles beyond the scope of the general medical reader. The two articles on polyoma, by Stewart and Eddy, are of great general interest, however, as is Smorodintsev's review of the difficult but important subject of non-specific resistance to viruses and Warren's account of the relationship between measles, canine distemper, and rinderpest. The other articles, such as the fine review of the structure of small viruses by Klug and Caspar, are rather more specialised. Virology stands at the centre of biological science where physical and chemical techniques are making their biggest impact on biological problems. This is why such first-rate review volumes are of immense importance in making accurate comprehensive accounts of virus work available to workers in related disciplines.

Surgery of the Aorta and its Branches

JAMES D. HARDY, M.S. (Chem.), M.D., F.A.C.S., professor of surgery, University of Mississippi. Philadelphia and Montreal: J. B. Lippincott. London: Pitman Medical Publishing Co. 1961. Pp. 386. 52*s*.

THE past years' knowledge of the surgery of the arteries has been gradually consolidated. Old and classical contributions can now be fully appreciated, while the surge of technical achievement has perhaps at last begun to slow. This is then a good time for reflection and review; arterial surgery may safely be said to have come through its trial and to have established itself. Perhaps with some relief, therefore, readers may now turn away from the jostling of original papers and contemplate with satisfaction a more mature and dignified consideration of the subject.

Fortunately, Dr. Hardy has concerned himself with what is now known and established. He has avoided any diffuse or speculative sections on the pathology of arterial disease, which, it must be admitted, seems as far from any general understanding as it was during the lively controversy a hundred years ago between the schools of Rokitansky and Virchow. Clinical, regional, and technical aspects of arterial disease are fully and clearly dealt with. There is an excellent review of the literature, and several hundred references, which, when used with the guidance of the book itself, will provide the complete survey of arterial surgery which has hitherto been hard to find for those working away from a university medical library. The sections on mesenteric and renal arterial occlusion are particularly valuable in this respect. Apart from the isolated criticism that the legend of fig. 37 does not seem to apply to the diagram above it, we can find little fault with this book. It is handy in size, clearly printed, and well illustrated. It is good value for money, and should be assured of success.

Assessment of the Activity of Disease

J. S. LAWRENCE, M.D., M.R.C.P., director, Empire Rheumatism Council Field Unit based on the University of Manchester. London: H. K. Lewis. 1961. Pp. 250. 42*s*.

MOST of this book is a very detailed analysis of the meaning and technique of the erythrocyte-sedimentation rate. No such comprehensive treatise on the subject has appeared in English for the past forty years; and (despite a certain amount of interesting background information and some useful data collected in this volume) it is not hard to see why. To look at disease as reflected in changes in E.S.R. and gross alterations in plasma-protein pattern with only marginal reference to clinical features and other more specific laboratory tests is like trying to survey a vast landscape through an old-fashioned photographic view-finder—a virtuoso performance rather than a practical exercise. Compressed and austerely factual in style, the book may not appeal to most clinicians or laboratory workers; but those with a special interest in the interpretation of erythrocyte sedimentation will be pleased to have much previously scattered information collected in a single work of manageable proportions.

A Short History of Obstetrics and Gynecology

THEODORE CIÀNFRANI, M.D., associate professor of obstetrics and gynecology, Graduate School of Medicine, University of Pennsylvania. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 449. £5.

Professor Ciànfrani has written a short and readable history in which the major events in the development of the specialty are traced from its beginnings in primitive societies. A certain amount of general medical history is included to maintain perspective. Sufficient is said of anæsthesia, bacteriology, radiology, medicine, surgery, and pædiatrics to show the part they played in the progress of obstetrics and gynæcology. Several chapters are devoted to the history of particular aspects —e.g., forceps, ovariotomy, infection, vaginal speculum, operative gynæcology, and cæsarean section. The book, which is profusely and well illustrated, merits a place in the library of the clinician and in the university departmental library, where it will give the teacher excellent background information for his lectures.

The Day Hospital Movement in Great Britain

JAMES FARNDALE, B.COM., F.H.A., M.R.S.H., barrister-at-law, deputy house-governor, Bethlem Royal and Maudsley Hospitals, London. Oxford: Pergamon Press. 1961. Pp. 430. 84*s*.

AN interesting development in post-war medicine has been the growth of the day-hospital movement. The sordid overcrowding of mental hospitals, financial stringency, and the appreciation that many of the mentally sick did not need a 24-hour routine led to experiments in outpatient care, and it soon became clear that day hospitals had considerable therapeutic advantages of their own, quite apart from their administrative convenience. Housed usually in old converted premises, the day hospital was more readily accepted by the reluctant patient and led to less institutionalisation. During his year's study (1958–59) as research fellow in the University of Manchester, Mr. Farndale cast an administrative eye over 65 day hospitals and centres then running for psychiatric, subnormal, and geriatric patients and for physical rehabilitation. He considers finance, catering, drugs, and transport exhaustively, and half the book is given to detailed descriptions of the 65 places. One important observation is that this type of care is not necessarily cheaper.

Though the book is a useful reference to those about to start a day hospital (which includes many abroad, for this country leads the Western field), they may find the photographs uninformative and wish for a more concise statement. Clinical data, as may be expected, enter little, and we still do not really know how far day-care can take the place of ordinary hospitals, or, come to that, how many people could be as successfully handled by an outpatient department offering an emergency service and the full range of treatments. But one also wonders how long it will be before the shortage of night nurses forces the physicians to think in terms of day wards: given transport, many of the physically ill could surely be investigated, observed, and treated in this way.

Black's Medical Dictionary (24th ed. London: A. & C. Black. 1961. Pp. 1012. 38*s*.).—To revise a book of this kind is an exercise in selection, and in this edition Dr. W. A. R. Thomson has once again successfully held the balance between the old and the new. He has introduced sections on such subjects as barrier creams, enteroviruses, and phenylketonuria, but by judicious pruning of the out-of-date he has added only one page to the *Dictionary's* length. There are also notes on new drugs, including hypotensive and hypoglycæmic agents and griseofulvin. Among the sections which have been entirely rewritten are those on mental defectiveness, mental illness, otosclerosis, and poliomyelitis.

THE LANCET

LONDON 10 JUNE 1961

A New Postgraduate Centre?

AT the end of last week *The Times* announced that agreement had been reached between the Ministry of Health and the South West Metropolitan Regional Hospital Board to clear the way for a new Postgraduate Hospital Centre in Chelsea; and on Monday it returned to the subject in a leading article. This is, so far as we know, the first published information about a scheme for the regrouping of some of the special hospitals of London, with their associated teaching institutes, about which rumours have been circulating for some time.

According to the original story, one of our more spectacular millionaires had proposed that, in return for the sites of a number of small central hospitals, he should rebuild them all together on the site of an infectious-diseases hospital which was no longer essential. All that was true in this story, however, seems to be that an interesting new suggestion had been made for a place in which to bring together some of the postgraduate hospitals—concentration of which was recommended in the Gray-Topping report as long ago as 1945. The suggestion was in fact found to be impracticable, because a vast railway siding, next to the fever hospital, was not available as supposed. But the Ministry of Health, which had already reviewed some other possibilities, was not deterred from further inquiries; and after several places had been considered it was agreed that the best was probably the combined sites of the Brompton Hospital, the Chelsea Hospital for Women, the Royal Marsden Hospital, St. Luke's Hospital, and the Brompton Oratory Convent School. Certainly this area appears to have great possibilities.

Condensation of some of the scattered small special hospitals and their associated postgraduate institutes would have some obvious advantages, alike for the patients and for teaching. Catering, laundry, accounting, heating, pathological and X-ray services, and much else can be provided more efficiently for a grouped hospital than for a number of separate small ones; and for some time it has been felt that special hospitals ought if possible to be closely associated with general hospitals, or at least that related hospitals (e.g., for diseases of the lungs and of the heart) should be associated with one another. Indeed, the more one thinks about it, the more each specialty has links with other specialties. From the educational standpoint, medical and surgical techniques of the special kinds might with advantage be in closer contact—especially in London, which provides postgraduate education for doctors from the Dominions and from foreign countries where extreme specialisation cannot yet be practised. And from the standpoint of research, the small special hospital, which was so perfect an instrument sixty years ago, when individuals were developing their subjects on their own, is no longer the ideal place in an era when teamwork and the laboratory have taken the place of the singlehanded clinician or surgeon.

There are also possible disadvantages in the scheme. Efficiency and economy would be poor rewards for an amalgamation which led to loss of the pride and tradition of our medically great, though physically small, special hospitals; and a very large hospital can be a terrible thing. But, on the face of it, this is too big an opportunity to be thrown away: there is so much to be gained that it will be better to concentrate on avoiding the obvious dangers than to be frightened off by them. Clearly, to be sure of avoiding the disadvantages that might come of haste, there is need for careful thought and for discreet and sympathetic negotiation between the bodies concerned. For example, to group the hospitals and institutes appropriately would be important. On the proposed site, there is room for by no means all of them, and some might be better related to a general hospital than to each other. Some of the larger special hospitals and institutes are not involved in the present scheme; nor is the Postgraduate Medical School at Hammersmith. Indeed there might one day be an opportunity to form a second group on the site of Wormwood Scrubs Prison near Hammersmith Hospital: for the moving of the prison into the country, which once was only a dream, has been seriously mentioned in relation to prison rebuilding; and, by the time it moves, the deplorable difficulty of getting to Wormwood Scrubs may have been overcome by the building of the ultimately inevitable station on the Central Line. This means that a thoroughly appropriate grouping could now be made on the Chelsea site with more freedom of arrangement than would be possible if it represented the last and only scheme of developing special hospitals and postgraduate institutes.

The Ministry of Health, for their part, are to be congratulated on having brought this sensible project into the region of possibility: and we hope that everyone concerned—particularly those of the medical profession—will try to take it further.

Psoriasis

REVIEWING biochemical studies of psoriasis, TICKNER [1] characterises this as the skin disease which "has been more investigated than any other". He cites about a hundred papers, but the gloomy fact remains that little practical help has resulted from all this effort.

The idea that psoriasis may be a biochemical disorder is far from new, but the evidence is still meagre. Clinically, psoriasis is an inflammation, at times even pustular, but sterile. It is often familial and may appear for the first time at almost any age, although it is rare in infancy. There is no evidence that it is due to a specific organism: it is not contagious. It cannot be ranked with the diseases

1. Tickner, A. *Brit. J. Derm.* 1961, **73**, 88.

of allergy or autoimmunity, and it is not significantly related to other general maladies. It may be precipitated by an infection such as a streptococcal sore throat; but physical trauma, sunburn, and perhaps emotional turmoil may also bring on an attack. No other tissue is involved, except the joints in the rare psoriatic arthropathy; and even here the significance of the relation between skin and joint symptoms is disputed.

In pursuing the laboratory evidence of metabolic disturbance, almost any claim can be countered by a contradictory one. Some of these discrepancies may be due to inadequate methods of estimation or lack of appreciation of normal values. Disturbance of fat metabolism was one of the earlier possibilities to be examined. In a study of the effect of a preparation of unsaturated fatty acids on psoriasis, ENTICKNAP et al.[2] have found no change in the blood-levels of ten common lipids; these were initially normal, and there was no clinical improvement. A high phospholipid content in the scales of psoriasis was reported as long ago as 1929; and this has been confirmed by STEIGLEDER [3] and JARRETT et al.[4] DOGLIOTTI [5] found similar quantities in seborrhœic dermatitis, and some workers attribute the presence of phospholipids to lack of their utilisation for normal keratinisation. No enzymes capable of removing such substances have been detected in the epidermis, and their role remains undecided. Excess SH groups have been demonstrated histochemically in the parakeratotic epidermis of psoriasis; and this may be due to the failure of the normal formation of SS linkages. VAN SCOTT and FLESCH [6] have confirmed biochemically that SH groups are present in excess; but MAGNUS [7] has shown that this is not peculiar to psoriasis. Early workers had suggested that the total sulphur content of the psoriatic scale was high; but subsequent studies have shown that scales produced on healthy skin with ultraviolet light yielded similar figures. When methionine containing radioactive sulphur is given to patients with psoriasis, the sulphur makes a delayed appearance in the lesions and persists longer than in healthy skin—which seems at variance with the view that in psoriasis the growth of the epidermis is accelerated.

SCHMIDLI and PASCHOUD [8] reported low levels of water-soluble polypeptides in the lesions of psoriasis and later showed that the activity of several dipeptidases was significantly reduced. This was thought to be due to the presence of an unidentified inhibitor in psoriatic scales. FLESCH believes that arginine is relatively increased in such scales, although other workers state that their aminoacid composition resembles that of scales produced by ultraviolet irradiation. Arginase is found in normal skin, and is present in psoriatic scales in greater amounts than in plantar callus. It is an essential component of the urea-synthesising mechanism, and increased quantities of urea might therefore be expected on the surface of psoriatic skin: the reverse is true according to ROTHMAN,[9] but the scales seem to contain an arginase inhibitor.

TICKNER is impressed by the evidence that in psoriasis fusion of primitive keratin filaments is defective. ROE [10] extracted three kinds of protein (A, B, and C) from dispersates of psoriatic scales. A, she concluded, was a normal intermediate of keratinisation which disappeared when keratinisation was normally completed. B was a globular protein containing SH groups, probably mucoprotein, present only in traces in normal epidermis. C was a nucleoprotein probably representing remnants of the parakeratotic epidermal cell. TICKNER draws attention to the X-ray diffraction studies of SWANBECK [11] on the macromolecular organisation of epidermal keratin, showing that keratin is synthesised in filaments 100 Å in diameter. These aggregate laterally in bundles of 5 or 10 with a lipid coating 80Å thick. In psoriasis the filaments fail to aggregate, and TICKNER asks whether this inhibition is due to Roe's protein B possibly together with lowered aminopeptidase levels. Such failure might account for the increased lipid content, if the fibres in psoriasis are coated with lipid as in normal skin. He suggests that protein B may have enzyme activity and account for the increased arginase. He believes that systematic research into enzymes and components of normal and diseased skin will reveal the presence of a metabolic block in psoriasis, giving rise to the accumulation of a substance which inhibits normal keratinisation.

Others, too, have pursued the idea that the basic fault is in keratinisation; and of course scaling is a notable feature of the disease—but so is inflammation. If the primary defect is in the epidermis, the dermal vasodilatation and cellular infiltration must still be explained. Other diseases of keratinisation, such as ichthyosis and tylosis, are not inflammatory. If the psoriatic epidermis contains something which evokes a dermal response, it should be possible to demonstrate this. Could not a biological approach be made to show whether chemical mediators of inflammation exist in the lesions of psoriasis or in the blood? Are such substances influenced by the known remedies for the disease—tar, dithranol, mercury, or ultraviolet irradiation? If psoriasis is an epidermal lesion, does psoriatic arthropathy not exist? And why is the hair unaffected when the entire skin and all the nails are involved?

The skin of the tail of the rat shows two types of keratinisation: around the hair follicles there is a granular layer, but between them there is none. When vitamin A is applied to the rat's tail, a granular layer appears where formerly it was absent.[12] JARRETT and SPEARMAN [13] reasoned that, if a granular layer could be re-established in psoriasis, keratinisation might be restored to normal. They achieved this by local application of vitamin A, but only after treatment with triamcinolone had controlled the proliferation of the epidermis. In their early tests triamcinolone was given

2. Enticknap, J. B., Ryan, C. C., Lansley, T. S. *ibid.* p. 99.
3. Steigleder, G. K. *Arch. Derm. Syph., Berlin*, 1952, **194**, 296.
4. Jarrett, A., Spearman, R. I., Hardy, J. A. *Brit. J. Derm.* 1959, **71**, 277.
5. Dogliotti, M. *Hautarzt*, 1953, **4**, 17.
6. Van Scott, E. J., Flesch, P. *Arch. Derm. Syph., Chicago*, 1954, **70**, 141
7. Magnus, I. A. *Brit. J. Derm.* 1956, **68**, 243.
8. Schmidli, B., Paschoud, J. M. *Dermatologica, Basle*, 1955, **110**, 315.
9. Rothman, S. *Arch. Derm. Syph., Chicago*, 1950, **62**, 814.
10. Roe, D. A. *Ann. N.Y. Acad. Sci.* 1958, **73**, 977.
11. Swanbeck, G. *Acta derm.-venereol., Stockh.* 1959, **39**, suppl. 43.
12. Lawrence, D. J., Bern, H. A. *J. invest. Derm.* 1958, **18**, 261.
13. Jarrett, A., Spearman, R. I. *Brit. J. Derm.* 1959, **71**, 267.

by mouth, but later it was applied locally in an ointment incorporating a special form of vitamin A. This treatment seems unlikely to prove applicable in many cases, if only for the reason of expense; and no commercial form of this ointment is yet on the market. But JARRETT and SPEARMAN argue their case with a wealth of histochemical evidence; and the treatment is the first to have a logical rather than an empirical basis.

The Handicapped

IN the last twenty years or so, the position of handicapped children has changed. Because of the decrease in debilitating infections of childhood, the handicapped child takes up a greater proportion of the time of pædiatric departments; and because of more successful life-saving measures in infancy, many more of the severely handicapped children are surviving. As some diseases, such as tuberculosis and anterior poliomyelitis, decline, the type of disability has altered, and the child with multiple handicaps has come to the fore. Lastly, and most importantly for these children, the education authorities are beginning to recognise their educational need and future potential.

Today, instead of helping a normally intelligent child with a tuberculous hip or a flaccid paralysis of one limb, we may have to provide total care for a spastic child with a defect of sight and eye movements, possibly a hearing loss, a movement defect, epilepsy, educational backwardness, and an emotional disturbance, shared by other members of the family; or for a hydrocephalic child with spina bifida and flaccid paralysis of the legs, a urinary-tract abnormality, and an intelligence well above the average.

Thus one child may be under the care of several doctors, specialists, and educationalists. The work of these professional people may even be duplicated if the child is away at a residential school and is under one group of doctors during term-time and another in the holidays. It is not unknown for a child who has been given appliances at a residential school to be seen in the holidays by a different consultant who recommends an operation and entirely different appliances. With this lack of liaison, it is possible for a child to be admitted for surgery at a time of particular emotional stress, and thus sustain unnecessary psychological trauma. At the centre of conflicting influences, the parents may become worried and confused. Obviously there is need for one doctor to coordinate all the treatment; and, at first sight, this should be the family doctor. But in any family practice over a period of years there may be only one child with a particular handicap, and the practitioner may not have an opportunity to understand the whole problem or know the facilities. It would be a great pity if the child's own doctor ceased to take an interest and feel responsible; but many of these cases do require the regular attention of someone with a fairly high degree of specialist knowledge and skill.

What may perhaps be needed is a doctor who will make a special study of one type of handicap. In a small town, it might be a general practitioner working for several sessions on the staff of a local hospital. Again, an experienced public-health doctor might have the necessary contacts to run a service for all the children in his authority's area. In larger centres, a pædiatrician, a pædiatric neurologist, a physical-medicine specialist, or a surgeon might prove to be the right person. Whoever he is, the doctor in charge must not only be able to supervise and organise treatment and referral to consultants; he must cooperate with the education authorities over the child's education, and have a contact with the special schools, preferably as the medical adviser. He should be interested in all the research in his specialty, be free to attend conferences, and be willing to try any promising new form of treatment. He must be able to make an early diagnosis of each handicap—i.e., deafness. His clinic must be a training centre.

But if we are to have these special centres, it is essential that each child should find his way to the most appropriate. One possibility would be a large diagnostic and evaluation centre such as that run by Dr. FREDERICK RICHARDSON at the Johns Hopkins Hospital, Baltimore, which was set up after the problem had been studied by a special commission.[1]

Children with all types of disability—communication disorders, poliomyelitis, educational backwardness, and cerebral palsy—are sent to the centre for assessment. The child is seen by a team which includes a psychologist and a social worker, and the appropriate consultants. After a conference, a full report, with recommendations for treatment and education, is sent to the family doctor, the school service, and other interested agencies. The child is seen about once a year. In this way the whole child and his problem is assessed and treated, and not one particular aspect of his handicap.

For the child with a multiple handicap a visit to a diagnostic clinic would be especially valuable. But even he would probably benefit from continuous care at a specialised clinic dealing with his predominant syndrome; and another pattern of care would be for hospital and local-authority services to join forces to run a clinic. The hospital doctor could arrange treatment, drugs, and appliances, and the local-authority doctor provide clinic facilities, and arrange schooling, home-visiting, and housing. An asthma clinic, an epilepsy clinic, an enuresis clinic, or a clinic for the mentally handicapped could be geographically placed to deal with most of the children in an area. An essential member of team would be an educational psychologist; for only when a full report has been obtained on the child's educational and intellectual level and his emotional problems can his handicap be discussed with his parents. For some handicaps, such as some of the rarer speech disorders, a few centres in the whole country might suffice to ensure that all the children came under the care of a specialist who had made a study of their condition. For example, cases of flaccid paraplegia benefit enormously by learning to swim; but only in a few centres have they a chance to do so.

If clinics of this kind were held regularly, the family

1. Report on Diagnostic and Rehabilitation Centers for Handicapped Children, Maryland State Planning Commission 100, Equitable Buildings, Baltimore 2, Maryland, U.S.A. 1957. Pp. 30. 50 cents.

doctor would know where to seek advice and get expert help, both from an initial assessment and from periodical reviews. There is always some danger in encouraging the formation of more and more subspecialties; but the plain fact is that throughout the country there are always doctors who are giving most of their time to one rather restrictive subject, and making a success of it. For the handicapped child continuity of care and interest is very important; and, if it is to be provided by clinics, conditions should be such that doctors and social workers find it easy to stay in the same locality for many years—feeling that the progress of a deformed infant to a handicapped adolescent in industry is their own particular concern. At the same time, if personal doctoring is to mean anything, the clinic must share this concern with the family doctor, who bears final responsibility for seeing that the child gets every chance that can be got.

Annotations

WATER

THE complaints occasioned by the drought of 1959 were stilled only by the louder ones which followed the floods of 1960. Perhaps these succeeding years exaggerated the vagaries of our climate, but they demonstrated that we are still vulnerable to natural phenomena and were enough to move the Minister of Housing and Local Government to consider once again the problems of water conservation.[1] In the British Isles these are peculiarly difficult. We enjoy no wet and dry seasons. Every year Oban has more rain than Margate, but this is no guarantee that Margate will not be engulfed in an August thunderstorm or that Oban will not suffer weeks of drought. England and Wales have an overall surplus of water, but 90% of this runs to waste. Domestic and industrial consumption meanwhile rises every year, and especial point is added to the Minister's anxiety by the increase in agricultural irrigation. South of the Humber-Severn line the rainfall is not enough for the full growth of crops in five years out of ten. The go-ahead farmer has learned to make good this deficiency from any convenient source, with the result that in some places the streams sink to nothing in a drought, to the dismay of the herdsman and the angler downstream. Upland catchment areas are enclosed for the exclusive use of this or that city on a first-come-first-served principle. Competition for supplies is not limited to the surface, and water engineers have found that there is a limit to the number of deep wells that can be sunk in any one area.

The voluntary or compulsory amalgamations of water undertakings will in time guarantee the consumer potable water all the year round, but can have little effect on supplies of water as a raw material. To this end the Minister proposes to establish "water conservation boards" (the name is still undecided) each of which will serve a single river basin or a group of adjoining basins. Their duties will be manifold: to make and keep up to date a hydrological survey of their basins; to estimate the future needs of consumers; to prepare plans which will prevent floods and droughts and to undertake the necessary works. They will have to allocate water-supplies between contending claimants. They will adsorb the duties of the existing river boards as they affect drainage, pollution, fisheries, and navigation. This will all cost a lot of money, and it is suggested that most of this will come from those who abstract and use water. Because the exercise of these powers is likely to tread painfully on many tender corns, and because competition for underground sources may involve two adjoining river basins, there will be a central authority to coordinate and to settle disputes, and it is the Minister's intention that this duty shall be his (and his successors') and shall not be delegated to an ad-hoc body.

The plan is imaginative and, we believe, sound—so long as the Minister does not clip the wings of the birds when he has hatched them. The powers of the river boards today are considerable on paper; but (for example) in combating pollution they cannot prosecute without the Minister's permission—and this is given once in a blue moon. (As a result legal action to check pollution has to be undertaken by riparian owners or such a body as the Anglers' Cooperative.) If the new bodies are to be useful they must have power and the right to use it. To make the best use of available skill, and as a safeguard against local pressure, the Minister might consider setting up a corps of technical staff analogous to the Animal Health Division of the Ministry of Agriculture. There are obvious advantages in a man knowing his own river from source to sea, but too long a sojourn under one master is bad for any professional man. Hydrologists and experts on pollution are not two a penny, and we hope that the best use will be made of them.

These proposals are still being studied. They concern our profession not much more than any other citizens, but they may help to impress on all that in this rather tightly packed island water is no longer free as the air. No doubt they were saying much the same about the soil during the Heptarchy.

1. Water Conservation. Memorandum by the Ministry of Housing and Local Government, May 11, 1961.

TREATMENT OF LICHEN PLANUS

THE cause of lichen planus is still unknown, and its treatment is often difficult. Sometimes the disorder, even when extensive, clears rapidly and spontaneously, which undoubtedly accounts for the claimed success of bizarre treatments such as lumbar puncture and spinal irradiation. The traditional remedy is perchloride of mercury by mouth, but its efficacy has never been substantiated by a controlled trial. Oral arsenic, although undoubtedly helpful in some cases, has been almost completely abandoned owing to the danger of late skin carcinoma. In the past decade corticotrophin and oral corticosteroids have produced dramatic improvement. Kristjansen and Reymann [1] claimed for treatment with corticotrophin a 50% cure-rate in fourteen days, but half the cured cases relapsed on withdrawal of the drug. Systemic steroid therapy is now usually reserved for severe generalised cases. Hypertrophic lichen planus is not improved by corticotrophin or oral steroids, but injection of hydrocortisone acetate into the lesions will result in local atrophy and abolition of irritation.

Alexander [2] fortuitously discovered that 'Dipasic' (isoniazid aminosalicylate) favourably affected the course of lichen planus. In a group of 30 cases of lichen planus

1. Kristjansen, A., Reymann. *Acta derm.-venereol., Stockh.* 1955, **35**, 143.
2. Alexander, J. O'D. *Brit. J. Derm.* 1960, **72**, 355.

he gave alternate patients dipasic and a placebo tablet. A further group of 30 patients were treated with dipasic—these included the cases which had not responded to the placebo tablets. Arbitrarily 600 mg. was given daily for six weeks, followed by 300 mg. daily for a further six weeks; active local treatment was avoided. All cases were followed up for at least six months and some for over two years. No toxic side-effects were observed, and in many itching was rapidly relieved. Of the 41 patients with lichen planus who completed the course of dipasic treatment and were adequately observed, 32 responded well; whereas of 14 controls only 5 showed a similar response. 4 of the treated cases and 8 of the controls showed no response whatever. Of these 8 control cases 4 responded well to dipasic, administration of which was begun not less than three months after the placebo tablets were stopped. The acute generalised type and the more localised chronic type responded better to dipasic than the hypertrophic or oral types. Of the 41 cases that were followed up, 6 relapsed after apparent cure but all responded to further treatment with dipasic.

Alexander could not explain the action of dipasic. Although suggestion may play a part in the improvement of some cases of lichen planus, this could hardly account for the success-rate of about 80% in Alexander's series. Further trials will be necessary to confirm these findings, and to establish the optimum dosage and duration of treatment.

EFFECTS OF RADIATION

FOR many years after Hiroshima and Nagasaki much of the research on the effects of ionising radiations was naturally concentrated on the results of sudden whole-body exposure. But in a world that was likely to rely more and more on atomic power, the ultimate effects of low doses, slowly absorbed, clearly needed fuller comprehension. Three new reports [1] from the United States National Academy of Sciences reflect the increasing research effort directed towards these chronic effects that are so hard to investigate.

The study of the association of radiation with leukæmia has been more exact than other inquiries because a fatal condition lends itself to mortality comparisons: the subtle and indefinite changes of premature ageing, another possible effect of radiation, are far harder to assess, particularly since physiological senescence is itself ill-understood. The epidemiological investigations—vast animal experiments and prospective inquiries on people whose occupation involves exposure to low doses—are complementary methods which may eventually show whether average life expectancy is reduced: but so many variables are involved that the answer may be a very long time coming; and the application of animal data to man is full of uncertainty. A prospective inquiry benefits from the fact that most of the nuclear agencies and X-ray departments in the United States and Great Britain keep careful medical and radiation exposure records of their employees. The larger the sample the better, and if it were possible to adopt common methods of measurement and recording throughout the world, much valuable information might be obtained. Differences which might be hidden when manifold recording methods allow only indirect comparisons might be revealed under standard conditions and suggest important new ideas. There seems to be a case for an international meeting of radiation-medicine and epidemiological experts to consider how to exploit such an opportunity.

For many years, those engaged in radiation work have regularly had white-cell counts, despite the unsuitability of this index for testing any but the grossest change, and despite considerable evidence that the hæmopoietic system shows no detectable damage until doses of the order of 100 rads have been received in a short time. A routine blood examination has the merit of establishing some measure of an individual's normal range of variation, in case he should be involved in a disaster: but as a warning that low doses are doing harm it has no value. The National Research Council's subcommittee on the effects of ionising radiation on the human hæmopoietic system declares: "Routine annual hematologic studies of occupationally exposed persons are useful only in establishing base-lines for following such persons. These studies are wasteful and unproductive in detecting low-dose radiation effects."

The best treatment of the acute radiation syndrome is in most particulars generally agreed upon: the one controversial point is the value of bone-marrow therapy. If the normal immunological response has been almost completely suppressed by radiation, it may be possible, by marrow transfusion, to tide a patient over temporary failure of the hæmopoietic system. On the other hand, there is a risk of a foreign tissue reaction, which could prove fatal to anyone seriously ill. If the dose of radiation is known to be so high that the patient faces almost certain death, it is justifiable to grasp at any straw: and the subcommittee advises that this should be the indication for giving bone-marrow therapy. As far as present knowledge goes this advice is wise; but it is to be hoped that experimental work will soon permit more room for clinical manœuvre.

EPILEPSY AFTER CLOSED HEAD INJURIES

WE are slowly learning more about the association between closed head injuries and subsequent epilepsy. A question of medicolegal importance (especially in view of the increase in road casualties) is how long the interval may be between the injury and the onset of epilepsy. Phillips [1] showed that in most cases of post-traumatic epilepsy the onset was within two years of injury; thereafter a causal association between the two must be regarded as more doubtful. Jennett and Lewin [2] find that the incidence of epilepsy is especially high after depressed fractures and subdural hæmatomas, and in patients under 5 or over 65 years of age. They find, too, that after early post-traumatic epilepsy (within a week of injury) persistent fits are especially common—occurring in 28% of such cases compared with 7% of those without early epilepsy. A similar finding was recorded in cases of epilepsy following penetrating brain wounds by Whitty,[3] who educed a family history of epilepsy as an additional predisposing factor. Traumatic epilepsy poses theoretical questions on cerebral function. Why should it develop in some people but not in others after seemingly similar injuries? Why should it start early in some and much

1. National Academy of Sciences: National Research Council Publications 848 (Effects of Inhaled Radioactive Particles), 849 (Long-term Effects of Ionizing Radiation from External Sources), 875 (Effects of Ionizing Radiation on the Human Hemapoietic System). Obtainable free from Printing and Publishing Office, National Academy of Sciences, National Research Council, 2101, Constitution Avenue, Washington 25, D.C.

1. Phillips, G. *J. Neurol. Psychiat.* 1954, **17**, 1.
2. Jennett, B., Lewin, W. *ibid.* 1960, **23**, 295.
3. Whitty, C. W. M. *Brain*, 1947, **70**, 416.

later in others? And why should it occur more readily after injury of some regions of the brain than of others?

PSEUDOTUMOR CEREBRI

THE term "pseudotumor cerebri" is commonly applied in the United States to the clinical syndrome which in this country is more often referred to as otitic hydrocephalus, benign intracranial hypertension, toxic hydrocephalus, or serous meningitis. This disorder is marked by protracted increase in the intracranial pressure, but focal neurological symptoms and signs are lacking and the cerebrospinal fluid is normal.[1] The most prominent symptoms are headache and blurred vision, while diplopia due to unilateral or bilateral sixth-nerve palsies is common; tinnitus, nausea, and vomiting are less usual. Bilateral papillœdema is invariably present, and its severity may be unexpected in view of the patient's apparent well-being. Consciousness is never disturbed, but in a small proportion of cases the papillœdema may be so severe as to threaten vision. This condition can never be safely diagnosed on clinical evidence alone: ventriculography is an essential step in differential diagnosis as some patients with intracranial neoplasms present with an identical clinical picture.

The syndrome was first described by Quincke [2] in 1893, and in 1936 Davidoff and Dyke [3] found that in such cases ventriculography revealed a normal outline. It later became clear that meningeal inflammation was not a feature, there being no pleocytosis or increase of protein in the cerebrospinal fluid. Many of the earliest cases on record were associated with otitis media; and Symonds [4] coined the term "otitic hydrocephalus", suggesting that the condition probably resulted from thrombosis of intracranial venous sinuses, and that, if the sagittal sinus were involved, venous obstruction and impaired absorption of the cerebrospinal fluid might contribute to the rise in pressure. In recent years, because of chemotherapy and antibiotics, fewer and fewer cases have been described in association with otitis media: Foley [5] in 1955 reported 13 "otitic" and 47 "non-otitic" cases. While the syndrome occasionally follows head injury or complicates cachexia or malignant disease (when it usually results from sagittal-sinus thrombosis), the majority of cases nowadays are in women of child-bearing age, in whom it is commonly related to pregnancy or to menstruation.[5] Foley [5] pointed out that often the cerebral ventricles are reduced in volume. Hence he agreed with Dandy [6] that the condition must be due to (*a*) obstruction to the venous outflow from the cranium, or (*b*) dilatation of the arterioles, or (*c*) swelling of the brain itself.

While in some cases the unquestionable cause is intracranial venous-sinus thrombosis, which can be demonstrated by venography, cerebral œdema of undetermined ætiology is, it now seems, a more usual cause. Thomas [7] in 1933 described the case of a woman in whom generalised œdema, headache, and bilateral papillœdema developed with each menstrual period; and recent studies of the papillœdema which may occur in the Guillain-Barré syndrome [8 9] or after poliomyelitis [10 11] have suggested that cerebral œdema is responsible. A similar explanation has been advanced for the symptoms and signs of increased intracranial pressure which sometimes develop in Addison's disease.[12–14] These observations suggested to Paterson et al.[1] that the syndrome of "pseudotumor cerebri" might often be due to an endocrine disturbance. They report a series of 17 cases of the condition, all in women of reproductive age; there was often associated obesity or menstrual irregularity, or the condition developed during or shortly after pregnancy, and in 4 cases there was galactorrhœa. The urinary levels of 17-ketosteroids and of 17-hydroxycorticosteroids were usually normal, but Paterson et al. give cogent reasons for suggesting that physiological hyperpituitarism is often at least partly responsible for the cerebral œdema—though they add that "pseudotumor cerebri" is a syndrome of multiple ætiology.

The illness is, as a rule, benign and self-limiting, though it may persist for many months; but when, occasionally, papillœdema endangers vision, operative decompression is required. Paterson et al.[1] found that in 5 out of 6 cases of "pseudotumor cerebri" administration of prednisone or methyl-prednisolone led to rapid improvement, and it seems justifiable to undertake steroid therapy in proven cases of this disorder where no definite cause can be demonstrated.

AMMONIUM-CHLORIDE POISONING

AMMONIUM chloride is widely used in small doses as an expectorant and diaphoretic and in larger doses as a diuretic and in order to make the urine persistingly acid. In the U.S.A. it is also used for weight reduction and is incorporated in preparations sold directly to the public for this purpose. The *B.P.* dosage of ammonium chloride as a diuretic is 3–6 g. daily in divided amounts; but it may be administered in a dosage of up to 8 g. daily without producing more than mild asymptomatic acidosis.[15] The acidosis arises because a hydrogen ion (H^+) is released from the ammonium ion (NH_4) when ammonia (NH_3) from it is converted to urea by the liver. Ammonium chloride is therefore potentially toxic because of this release of hydrogen ions and because ammonia is itself toxic. The prevention of toxicity depends on good renal function, for the elimination of the hydrogen ions, and on good hepatic function, for speedy conversion of the ammonia to urea.

Two instances of ammonium-chloride poisoning in apparently healthy subjects are reported by Relman et al.[16] Both were in women, one of whom was attempting to slim; she took 82 g. of the compound in forty-eight hours. The symptoms were headache, nausea, vomiting, and hyperpnœa, with progressive drowsiness and confusion. The urine of both patients contained protein and was acid (pH 4·8 and 5·0) and of low specific gravity (1·010 and 1·001). Biochemical investigations revealed profound hyperchloræmic acidosis. Treatment with large amounts of intravenous sodium bicarbonate and lactate (691 mEq.

1. Paterson, R., De Pasquale, N., Mann, S. *Medicine, Baltimore*, 1961, **40**, 85.
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3. Davidoff, L. M., Dyke, C. G. *J. nerv. ment. Dis.* 1936, **83**, 700.
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8. Ford, F. R., Walsh, F. B. *Bull. Johns Hopk. Hosp.* 1943, **73**, 391.
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10. Weiman, C. G., McDowell, F. H., Plum, F. *Arch. Neurol. Psychiat.* 1951, **66**, 122.
11. Gass, H. H. *J. Dis. Child.* 1957, **93**, 640.
12. Boudin, G., Funck-Brentano, J. L., Gayno, M. *Bull. Soc. Méd. Hôp. Paris*, 1950, **66**, 1736.
13. Walsh, F. B. *Arch. Ophthal., N.Y.* 1952, **47**, 86.
14. Jefferson, A. *J. Neurol. Psychiat.* 1956, **19**, 21.
15. The Extra Pharmacopœia: Martindale; vol. 1, p. 1222. London, 1958.
16. Relman, A. S., Shelburne, P. F., Talman, A. *New Engl. J. Med.* 1961, **264**, 848.

in twenty hours in one patient and 643 mEq. in forty-eight hours in the other) produced rapid clinical recovery; but hyperventilation tended to persist rather longer than would have been expected from the biochemical data, and during treatment severe hypokalæmia developed after six hours. After recovery the proteinuria disappeared and the ability to concentrate urine reverted to normal.

In these two cases the dosage far exceeded that recommended; but there is evidence that with impaired renal, hepatic, or cardiac function less excessive doses may cause toxic manifestations. Symptoms of ammonium-chloride intoxication have been reported in patients with renal dysfunction who have taken as little as 5 g. daily.[17 18] It is known, too, that in severe liver disease the blood-ammonia level is raised,[19] and that, when this is so, hepatic coma may be precipitated by giving ion-exchange resins which act by releasing the ammonium ion and taking up sodium.[20] In chronic cardiac disease, ammonium chloride in dosages of 4 to 6 g. daily by mouth has been found to cause anorexia, hyperpnœa, lethargy, and drowsiness.[21] Accordingly ammonium chloride is contraindicated when there is renal or hepatic disease, and its use in the management of cardiac œdema should be undertaken with care. Courses of treatment involving more than 4 g. daily should always be intermittent; and if the patient becomes anorexic, dyspnœic, or lethargic the possibility of ammonium-chloride intoxication must be considered.

HOSPITAL PLANNING

"By the time a modern hospital is built it is already twenty years behind the times." Expressing this view at a London meeting arranged last week by King Edward's Hospital Fund, Mr. Gordon Friesen, a consultant in hospital planning from Washington, D.C., attributed the time-lag to a failure of basic policy in the planning of hospitals. The practice, he said, is to start with a somewhat sketchy idea of the function of the new hospital and its various departments, to put up a building of what is thought to be about the right size, and then, Procrustes-like, to adapt the organisation to fit the building. In other words, function is made to depend on structure, whereas in Mr. Friesen's opinion the organisation of the hospital should be planned in very considerable detail—including detail of fixed and movable equipment—before pencil is put to paper, beyond a scribble. Or, as he expresses it, "develop the organisation and put a roof over it".

In the United States 70% of the maintenance cost of a hospital is for salaries and wages (the figure in Great Britain is about 60%) and in both countries under present conditions the figure is likely to rise. If a good hospital service, therefore, is not to price itself out of existence, it must conserve labour, especially skilled labour, by applying to the utmost the method of automation borrowed from industry. Time-and-motion studies have shown that a high proportion of work at present done in hospital is non-productive, and that less of a nurse's time should, for instance, be spent in fetching and carrying. A bricklayer for generations has had a hod-carrier to mix his mortar and carry his bricks, enabling him to devote his whole energies to the skilled work of bricklaying. Is not a nurse as important as a bricklayer?

Mr. Friesen would adopt a conveyor-belt system for everything possible in a hospital except the patient: indeed he has done this in a number of hospitals on which he has been engaged in the U.S.A. By this means he claims that the savings in running costs will pay for the capital cost of the hospital in twenty years. (He estimates the annual maintenance cost at 40% of the capital cost.) His conception of the structure of a modern hospital is that the inpatient accommodation should be piled vertically, with 60 beds to a floor; the total bed-capacity is thus fixed at the outset. But the supporting services—outpatient accommodation, laboratories, X-ray department, theatres, and so on—are planned horizontally so as to give flexibility and scope for expansion as investigations multiply and special procedures are devised.

On the bottom floor of the vertically planned inpatient block is a central area for the mechanical washing and autoclaving of *all* soiled articles from the wards—instruments, bedpans, crockery, and linen (the laundry is adjoining). After being autoclaved, the articles are prepacked (linen packs, instrument packs, &c.) ready to be sent back to the wards by hoists fitted with automatic ejectors to eject packs at any required floor. Soiled articles and garbage for disposal ("trash") come down from the wards in appropriate hoists or chutes. All supplies, linen, drugs, crockery, hardware, and food are centralised. Pneumatic conveyor tubes are freely used for the circulation of mail and sending of reports, records, pathological specimens (in standard containers), and drugs from one part of the hospital to another. Whenever possible, equipment—laboratory benches, desks, refrigerators, and even shelves—is mounted on castors, for flexibility and ease of cleaning.

Inpatients are in rooms with 2 beds or sometimes 4. Each room has its own W.C. and shower (it is contended that by vertical planning this is not expensive) and communicates by microphone with the centrally placed nurses' station. Each patient has his own urinal and bedpan, which after use are placed in a small compartment off the patient's room by a nurse who then calls on the microphone for an attendant to take it away and send it to be emptied, cleaned, sterilised, and replaced. With soiled linen the procedure is similar. Patients' meals, selected from a menu, are prepared by the dietitian staff in the central kitchen and sent up ready served on a tray for each patient.

In commenting on these very interesting developments we have to admit that in Britain our thoughts on hospitals tend to be rather old-fashioned. But it does seem that some of Mr. Friesen's generally admirable precepts need to be treated with a dash of circumspection. A certain amount—not overdone—of repetitive work, to-ing and fro-ing, fetching and carrying, making-do and mending, is not without value in the training of the young student-nurse, who after qualification may find herself called on to nurse the sick under conditions where push-button automation and fingertip control are not within reach. Moreover the conveyor-belt philosophy, if carried too far, could produce a state of mind where mechanical efficiency replaced humanity. A Frankenstein monster would then have been created; and, despite our earnest intentions, the patient himself would be on the conveyor belt.

But, whether or not one agrees entirely with Mr. Friesen, one cannot but be carried along by his infectious enthusiasm; and the King's Fund is to be thanked for making his voice heard last week by so many hospital planners in this country.

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Special Articles

EPILEPSY AND CAR-DRIVING

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MANY patients with epilepsy continue to drive though they have been advised very strongly against doing so. Some even drive to hospital for their outpatient visits. One young man who often had minor seizures said, as he was leaving the room one wintry day, " Pity me, doctor. Over an hour's drive home, in this weather! ". He rode a powerful motor-cycle.

To get a clearer picture of what was happening, patients with epilepsy who attended a neurological outpatient clinic were asked whether they drove, whether they possessed valid driving licences, and what they felt about the matter of their driving. The results of the inquiry, which lasted three months, are presented here.

The Inquiry

The Patients

130 patients over the age of seventeen were questioned —70 women and 60 men. All were liable to recurrent attacks of epilepsy. Patients under investigation for epileptic attacks of recent onset were not included. The numbers do, however, include the mentally defective and demented, and patients with hemiparesis or other physical defect. Though at first it seemed reasonable to restrict the inquiry to those otherwise *likely* to drive, it soon became clear that in practice no such division could be made. For instance, one moderately demented epileptic with a spastic paraparesis was found to be driving his own car regularly and apparently quite skilfully.

The patients were reassured that the inquiry was not an effort to catch them breaking the law, and their answers were probably fairly truthful. Each was asked whether he (or she) drove, and whether he had a valid driving licence. If he neither drove nor had a licence, he was asked about driving and the possession of a licence in the past. If he had a licence, he was asked how he filled in the form of application, box 12 (" Do you suffer from epilepsy, or from sudden attacks of disabling giddiness or fainting? "). Everyone who drove was asked what he felt about his fitness to be on the road, and the danger to himself and other people, &c. All were questioned about accidents when driving, and whether these had been attributed to the epilepsy or not.

Results of the Inquiry

Women.—Of the 70 questioned, only 1 drives, and she possesses a valid licence obtained by filling in the form untruthfully. 8 women had had driving licences in the past but had allowed them to lapse, probably because of the epilepsy, though at least 3 of them must have taken out licences after the epileptic attacks had begun. None admitted having had an accident when driving.

Men.—27 of the 60 drive or hold valid driving licences. None of these admitted to any accident while driving which could be attributed to the epilepsy, though several had had attacks when driving (see below). None had had, under any circumstances, a serious accident in which someone was injured. The figures can be further broken down.

The 27 men who drive or possess licences:

3 patients have licences, which they renew by filling in the application form untruthfully, but they say that they do not drive. They continue to take out the licence because they fear that if it is allowed to lapse they may have to take the driving test again, and they hope that in the future they will be free of attacks and able to drive safely. All 3 possess cars, but 1 has suspended its insurance " until I have got rid of the attacks ".

2 patients started to have epileptic attacks since taking out the new-three-year licences, and they do not know what they will do when the time comes for renewal. Both continue to drive.

1 patient renews his licence in Eire, and he continues to drive here.

1 patient had filled in the application form truthfully, stating that he suffered from epilepsy. He requested special medical examination, which he had, and he seems to have been treated courteously by the local taxation officer. He said that he had nocturnal seizures only, and was issued with a licence. In fact, he has diurnal seizures also.

2 patients say that they have always filled in " yes " against question 12 in the application form, and the licence has been renewed without question.

2 patients drive regularly, but do not take out driving licences. They are afraid of filling in the application form untruthfully, and prefer the risk of a small fine for driving without licence.

16 patients fill in the application form falsely. Several made a stand on the literal wording of question 12, saying defensively that they did not " suffer " from their epilepsy. 3 with only minor attacks said, probably truly, that neither by the hospital nor by their own doctor had they been *told* that they suffered from epilepsy.

The 33 men who neither drive nor hold licences:

3 patients had handed in their licences voluntarily to the local taxation office on being told by a doctor that they should not drive.

5 patients had allowed their licences to lapse.

2 patients had had driving licences when they were in the Forces during the war, but had never taken out civilian licences.

1 patient was refused a licence, though he had been free of attacks for three years, after filling in the application form honestly and stating that he had had attacks of epilepsy.

22 patients had never driven or possessed driving licences.

Comment by the Patients who Continued to Drive

Almost without exception those who continued to drive insisted that they would never have an attack when driving, or that they " always had enough warning ". Several patients righteously described what they felt were entirely adequate warnings that they had had when driving, and which had given them ample time to draw into the side of the road in case the attack progressed to loss of consciousness. One man gave an instance:

He said that he had felt an attack coming on, and had drawn in to the kerb where a police constable was standing. He got out of the car, handed the car key to the policeman, said that he was going to have a fainting attack, and lay down on the pavement. He returned to consciousness in the casualty department of a hospital, with the policeman by his side, who said, " You know, I didn't really believe you when you lay down on the pavement." He escorted the man back to his car, and watched him drive off.

All the patients said that if they should ever have an unheralded attack when driving, or have an accident due to an attack, they would certainly give up driving at once.

Many quite sincerely believed that they would never have attacks when driving, and that they were not placing themselves and other road users at risk. Others were troubled by guilt and very much on the defensive. A few were exceedingly bitter about this further social and legal imposition on them as epileptics: two said it would be " just as well " if they met with

serious accidents and were killed. Inquiry into whether they thought it right that they should continue to drive often tapped this reservoir of bitterness in intelligent patients. Clearly most felt that this restriction was too unfair to be tolerated, and that they *were* justified in going on driving, risk or no risk. Time and again a man would ask, resentfully, what he could do if he stopped driving: he would lose his job, and his family would suffer. He was not prepared to stop unless an attack when he was actually driving showed that the danger was real. Again and again the point was made that it was unfair to expect a man to ruin his life because he *might* have an attack when driving.

Discussion

Though small, this sample is probably fairly representative of the well-controlled and moderately controlled epileptic population. The striking thing is that nearly half drove or had valid licences. If some approximate adjustment is made for the inadequate, the unemployable, and the younger patients still being looked after at home very much as children, probably two-thirds of the men capable of driving did so. If they are to be believed, none of them had had any important accident when driving: this would be a remarkable enough finding in any comparable group of " normal " drivers.

The point of practical importance is that these men do not intend to stop driving. Because it is important that they should, ought steps be taken to see that they do? It seems only common sense that a man liable to episodes of altered consciousness should be forbidden to drive, yet we must bear in mind that such a prohibition may fall unfairly on the epileptic because of the very notoriety of his complaint. The man whose coronary circulation is precarious must be at least as dangerous a driver, but he is as yet under no obligation to give up his licence even after a frank infarction.

There is no reliable information to guide us on the incidence of epileptic attacks as a cause of traffic accidents, and this is unlikely to be forthcoming. While the healthy driver is only too ready to attribute his failure to a momentary " blackout ", the epileptic driver on the contrary will keep quiet about a lapse of consciousness which might bring to notice his illegally obtained licence, with all the consequent difficulties about insurance.

At present all the doctor can do is to advise his patient to give up driving, and perhaps try to influence the decision through other members of the family. He can do no more. The patient holds his licence perfectly legally until the time comes for its renewal, when he must declare his disability. With the new three-year licences, this may be for quite a long time. The local authority has power to revoke a driving licence when satisfied that by reason of disease or physical disability the holder is a danger as a driver, but in practice there would have to be an accident demonstrating the disability before this could happen.

The position seems to be that a high proportion of epileptics will continue to drive, and they will do so despite advice to the contrary from their doctors. The only practicable way of stopping them would be the abhorrent one of requiring notification of epilepsy to the licencing authority, as in some areas in the United States. On the other hand, as far as this small study goes, there is no indication that these patients are any more liable to accidents than other people. The observations give no great cause for worry.

I am grateful to the medical committee of the Maida Vale Hospital for Nervous Diseases for permission to publish these findings.

GENERAL MEDICAL COUNCIL

SESSION MAY 30 AND 31

Sir DAVID CAMPBELL's presidential address to the Council was summarised in last week's issue (p. 1222).

REGISTRATION OF POSTGRADUATE QUALIFICATIONS

The Council accepted a report by a special committee which expressed the hope that Parliament would agree to correct the anomaly by which persons obtaining certain postgraduate qualifications in the British Isles occupy an inferior position, so far as the registration of such qualifications is concerned, to persons who have obtained analogous diplomas in Commonwealth and foreign countries.

In its report the special committee remarked that part III of the Medical Act of 1956 empowered the Council to register at its discretion higher or additional qualifications granted in Commonwealth or foreign countries with which reciprocity exists. By contrast the Council is not empowered by part II of the Act to register any higher or additional qualification granted in England, Wales, Scotland, or Ireland unless it is directly specified in the third schedule to the Act. This schedule reproduces with relatively minor amendments schedule A to the Medical Act of 1858. Thus, while the Royal College of Obstetricians and Gynæcologists is entitled to choose a member of the Council, the Council is not empowered to register any of the college's qualifications, because the third schedule mentions neither the college nor its qualifications.

PHARMACOPŒIA COMMITTEE

Lord COHEN OF BIRKENHEAD said that the *British Pharmacopœia* Commission had discussed the adoption of an abbreviation of " microgramme ". Sometimes μg. and γ was used, but neither was suitable. There was a danger in typography " and certainly in doctors' writing " of confusion with other abbreviations. The Commission recommended the adoption of " mcg. " because this was less likely to be mistaken for other abbreviations; it was already used in some countries and had been adopted by the *United States Pharmacopœia*. It was proposed to use " mcg." in the next edition of the *British Pharmacopœia*, and the Commission stated in its report that it would welcome the general adoption of this abbreviation in medicine and pharmacy.

MEDICAL CURRICULUM

The PRESIDENT submitted the report of the special committee on the medical curriculum, appointed to consider reports received from licensing bodies and medical schools.

The Council's 1957 Recommendations as to the Medical Curriculum were devised with the main aim of reducing the congestion in the curriculum. Much of the detail which had hitherto appeared in the Recommendations was removed, and licensing bodies and medical schools were recommended to experiment freely with different courses and examinations and with various methods of teaching.

The committee says that statements on policy by licensing bodies and medical schools " bear witness to a wide variety of experiments already in progress or in contemplation ". The committee was glad to note in particular the finding of the University of London that " the degree of flexibility in medical education encouraged by the new Recommendations is a particularly welcome feature in this federal University as it offers the opportunity to include in Degree Regulations a number of new provisions that will enable Medical Schools to exercise certain options with their teaching arrangements ". Many schools have welcomed the new latitude with regard to the arrangement of courses and are planning integration of courses and teaching, although some regret has been expressed that it has not been found possible to proceed more rapidly with the development of " internal " examinations.

Basic Sciences

There is concern at the lack of adequate training in certain aspects of the basic sciences of some students who enter the preclinical course direct from school. Various plans suggested or adopted to remedy this deficiency include: (1) a voluntary course in medical physics, with emphasis on radiation, special optics, electronics, and other matters of special interest in medicine; (2) a special course in organic chemistry in the preclinical period, in order to bridge the gap between chemistry at G.C.E. advanced level and biochemistry; and (3) instruction in biology, to continue throughout the clinical course (examples of subjects to be taught in the clinical period are human genetics, immunology, and radiobiology).

Anatomy, Physiology, Biochemistry, and Related Subjects

One university has decided to include the whole of the course in anatomy in the first preclinical year, during which histology, human biology, and organic chemistry will also be studied. The examination in these subjects will be held at the end of the first year. Physiology and biochemistry will be taken in the next year, together with psychology, pharmacology, and elementary pathology.

A suggestion has been made that the written and practical portions of the second M.B. examination should be abolished and replaced by a faculty assessment of the candidate's record of class work, supplemented by an oral examination.

It is evident that there is a welcome increase in the interchange of teachers in the clinical and preclinical subjects, and in the institution of combined lectures and demonstrations.

Clinical Studies

Resident clerkships.—Many schools wish to increase the period spent in residence in hospital in the various clinical departments. For example, one university intends to arrange for its students to spend at least two months as whole-time clerks in clinical pathology; and three schools propose to introduce a period of (say) one month to be spent in residence in a mental hospital or as a whole-time appointment in the study of psychiatry.

Free time.—With the reorganisation undertaken under the revised Recommendations, it has been found possible to allow students in the clinical period to have some free time before the final examination.

Elective courses, appointments, or periods of study.—A number of universities and schools have decided to give to each student, at some stage in the clinical period, an opportunity to pursue intensively one or more special subjects, either by supervised research, by attending special lectures, by holding an appointment, or by other methods of study.

Tutorial System

Some universities and medical schools have introduced a system by which students are attached to members of the staff acting as tutors to advise on academic and personal problems.

New Curriculum Suggested by One University

The committee finds of some interest a proposed new curriculum based on the 1957 Recommendations, though, says the committee, the number of examinations may militate against the integration of studies. In this curriculum it is proposed that the preclinical period proper shall be reduced to three terms. There will follow a year in hospital with systematic and clinical medicine and surgery, pathology, and bacteriology, and then a year of " integrated studies ". During this year the various systems of the body will be studied in turn. The outline of the proposed curriculum is as follows:

First year, " premedical ".—In the first two terms physics, chemistry, and biology, with an examination in physics and biology in March; in the third term chemistry and anatomy, with an examination in chemistry in June.

Second year, " preclinical ".—Anatomy, physiology, and biochemistry, with an examination in these subjects in June.

Third year, " paraclinical and clinical ".—Physiology, pathology, bacteriology, systematic medicine and surgery, clinics, with an examination in June in pathology and bacteriology with physiology.

Fourth Year, " integrated studies " (preclinical, paraclinical, and clinical).—These studies, undertaken partly in the preclinical departments and partly in hospitals, will include applied anatomy and physiology and clinical biochemistry, together with materia medica. There will be an examination in June in all these subjects.

In the *fifth year* " specialty classes " will be held during the first two terms in public health, medical jurisprudence, psychological medicine, and the special clinical subjects. There will be an examination in March in public health and medical jurisprudence. " Intensive studies ", including periods of residence in medicine, surgery, and obstetrics, will commence in the third term.

In the *sixth year* " intensive studies " will continue during the first two terms, but the third term will be left for revision before the final examination in June.

Medical Disciplinary Committee

The committee met on May 31 and June 1, under the chairmanship of the President.

CASES CLOSED

The committee determined that the Registrar should not be directed to erase the names of *Gerald Francis Adye-Curran*, M.C., L.R.C.P.I. (1934), registered as of 4, Park Place, Liverpool, *Norman Thomas Brown*, M.B. St. And. (1923), registered as of 331, Bowes Road, New Southgate, London, N.11, and *George Horace Tancred Williams*, M.R.C.S. (1938), registered as of S.S. *City of Birmingham*, c/o Mail Office, Ellerman Lines Ltd., 18–20, Camomile Street, London, E.C.3. Judgment in these three cases had previously been postponed.

CASES POSTPONED

The committee was still not satisfied that the evidence so far received would warrant it in discharging at the present time the case of *Richard Maurice Dooley*, M.B. Dubl. (1945), registered as of 74, Eglinton Road, Donnybrook, Dublin. Judgment had been postponed for one year in November, 1959, following convictions involving drink, and in November, 1960, judgment was further postponed for six months.

Florence Berchmans Lawlor, M.B. N.U.I. (1936), registered as of 35, Belsize Park Gardens, London, N.W.3, had had judgment postponed for one year, until November, 1960, following convictions of being in charge of a motor-car when under the influence of drink and of unlawfully obtaining drugs by false pretences, and last November judgment was further postponed. Judgment was postponed for a year, until May, 1962.

In the case of *Michael Ambrose Owen*, M.B. Wales (1951), registered as of 49, Bro-Deg, Cwmbach, Aberdare, Glam., due to appear for postponed judgment, the committee postponed judgment for a further period of a year.

John Anthony Perpoli, M.C., L.R.C.P.E. (1939), registered as of 11, Bank Street, Hillhead, Glasgow, W.2, due to appear for postponed judgment following convictions in 1939, 1958, and 1959 involving drink, was not present. The committee postponed judgment until its November session.

INTERIM APPEARANCES

Peter Louis Milbourne Hartley, M.R.C.S. (1941), M.B. Camb. (1946), registered as of 408, Wimbledon Park Road, London, S.W.19, had had judgment postponed for two years, with a requirement for an interim appearance at this session. The committee confirmed its decision to postpone judgment until May, 1962.

Gerard Joseph McCann, L.R.C.P.E. (1949), registered as of Laurel Bank, Woolton Road, Liverpool, 16, made an interim appearance. Judgment had been postponed for two years following drink convictions. The committee continued consideration until May, 1962.

The committee noted the evidence as to the conduct of *Robert Walter Simmons*, M.B. N.U.I. (1942), registered as of Hertford County Hospital, Hertford, Herts, against whom judgment had been postponed for two years, subject to an interim appearance.

ERASURES

Alan Robert Ellerker, L.M.S.S.A. (1947), registered as of 5, Idmiston Road, West Norwood, London, S.E.27, was charged with having been convicted on Aug. 23, 1949, at the Birmingham City Magistrates' Court of being in charge of a motor-car when under the influence of drink; of being convicted at Melbourn (Cambridgeshire) Magistrates' Court on

Nov. 30, 1959, of driving a motor-car when under the influence of drink; and of being convicted on Dec. 20, 1960, at the Leyland Hundred Magistrates' Court of driving a motor-car whilst disqualified and of driving when under the influence of drink.

Mr. G. J. K. Widgery, solicitor to the Council, said that Dr. Ellerker had been conditionally discharged at Boston Magistrates' Court on May 16, 1952, for obtaining £2 by false pretences. He had also been conditionally discharged for other offences in the same year. His name was erased under Section 14 of the Medical Act, 1858 (now Section 41 of the Medical Act, 1956) because he did not answer letters from the Registrar. In October, 1956, whilst his name was off the Register, he was convicted at Darlington Magistrates' Court of obtaining credit by paying a hotel bill with a worthless cheque and obtaining money by fraud by worthless cheques; further similar offences were taken into consideration and he was sentenced to twelve months' imprisonment. As he was not on the Register he was not charged with these convictions. In 1957 he was put on probation at Newmarket Magistrates' Court when he pleaded guilty to stealing £3 from a till in a garage, further offences of obtaining credit being taken into consideration. On Nov. 23, 1959, he appeared before the executive committee of the Council and appealed for his name to be restored. He had made three previous applications, but on this occasion he knew of the Melbourn case but did not inform the executive committee. His name was restored on Nov. 23, 1959, but since then there had been these further convictions.

By reason of the convictions proved against Dr. Ellerker, the Registrar was directed to erase his name from the Register. Dr. Ellerker has twenty-eight days in which to appeal.

Alfred Francon Williams, M.B. Edin. (1940), registered as of 18, Crabtree Lane, Sheffield, 5, was charged that on Jan. 12, 1961, at the City of Sheffield Magistrates' Court he was found guilty of being found drunk in a public place, and that at the same court on March 13 he was found guilty of being drunk and disorderly in a public place and of causing wilful damage to property.

Mr. Widgery said that Dr. Williams last appeared at the November session, because of two convictions for drunkenness in July and September, 1960. He was before the committee in November, 1959, in respect of two earlier convictions: the case was concluded and his name was not erased. Within the past two weeks there had been a further conviction for driving a motor-car while under the influence of drink, when he was sentenced to four months' imprisorment, but that conviction was under appeal.

Announcing that the committee had directed the Registrar to erase the name of Alfred Francon Williams, by reason of the convictions, the President said: "The committee wish me to say that if you come before them again cured of your addiction to drink, an application for the restoration of your name will be sympathetically considered." Dr. Williams has twenty-eight days in which to appeal.

David Howard Hiley, registered as of 13, Warham Road, South Croydon, Surrey, M.R.C.S. (1942), was charged that he formed an improper association with a married woman, as a result of which she left her husband, that from March 7, 1960, he had lived with her and frequently committed adultery with her, that he stood in professional relationship with the woman at the material times, and that in relation to the facts alleged he had been guilty of infamous conduct in a professional respect. Mr. Widgery said the case was unique in that the first information about the charge came to the notice of the Council in a letter written by the practitioner in which he confessed to adultery with a woman patient. The committee found the facts proved and that Dr. Hiley had been guilty of infamous conduct in a professional respect. After deliberation in camera the Registrar was directed to erase the name of David Howard Hiley. He has twenty-eight days in which to appeal.

CASES DISMISSED

When *John Edwin Harpham Griffiths*, M.R.C.S. (1942), registered as of 10, The Esplanade, Douglas, Isle of Man, was charged with having behaved improperly to and committed adultery with a woman patient, Mr. Widgery said he could not proceed with the case because the witnesses had declined to come and give evidence. They were resident in the Isle of Man, and the powers of the committee to issue subpœnas could not be exercised because the Judicature Act did not extend to the Isle of Man. The complaint was brought by the husband of the woman. Mr. Widgery said he had in mind requesting an adjournment of the inquiry to the Isle of Man as there was provision for holding inquiries elsewhere than in the Council's house, but even then they could not insist on the witnesses attending. In the absence of any evidence to support the allegation the committee found that Dr. Griffiths was not guilty of infamous conduct in a professional respect in relation to the facts alleged against him in the charge.

Loh Mung Sun, L.R.C.P.E. (1917), registered as c/o The Chartered Bank, Raffles Place, Singapore, 1, was charged with infamous conduct in a professional respect as a result of a conviction in the High Court of Sarawak, North Borneo, and Brunei at Sandakan, for an unnatural offence against a male patient, for which he was sentenced to twenty-two months' imprisonment and ordered to pay the costs of the prosecution with an alternative of a further three months' imprisonment. Dr. Sun was not present and was not represented.

Mr. Widgery explained that as this was a conviction outside the British Isles he had to proceed with it as a case of infamous conduct and prove the facts alleged in the conviction. This he would do by reference to the transcript of the trial (from copies of which, handed to the members of the committee, parts which would have been inadmissable in a United Kingdom court were excluded).

The Legal Assessor said it was laid down in the Spackman case that, where there was a finding of a court of competent jurisdiction on a question of fact, that finding itself might be regarded by the committee, and indeed must be regarded, as some evidence of the fact found, although it was not, as was pointed out in the Spackman case, conclusive evidence. In one respect the committee was in a better position than the trial judge, because some of the evidence in this case was highly technical. A very disquieting feature of this case which emerged from the judgment of the court of appeal was that at some stage the trial judge had a document which was prejudicial to Dr. Sun. In Borneo, apparently, they did not try cases of this sort with a jury. If the case had been tried in England the conviction would have been quashed. The court of appeal, upholding the conviction and sentence, said the trial judge studiously ignored the document. It was a very difficult thing to put out of one's mind once it had entered. The Legal Assessor dealt at length with the need for corroboration and examined the evidence in this respect. He said the only evidence which might be corroborative was the medical and technical evidence.

The committee determined that the facts alleged against Dr. Sun in the charge had not been proved to its satisfaction, and it accordingly found that he was not guilty of infamous conduct in a professional respect.

CONSIDERATION ADJOURNED

Roy Wilfrid Downie, M.B. Edin. (1950), registered as of 88, Comley Bank Avenue, Edinburgh 4, was charged with having been convicted on June 30, 1960, at the Wolverhampton Borough Magistrates' Court on six charges of unlawfully procuring dangerous drugs; and on Dec. 20, 1960, at the Rochdale Borough Magistrates' Court, of nine charges of unlawfully procuring dangerous drugs and two charges of failing to make entries in his dangerous drugs register.

Dr. Downie was not present. The Chairman announced that the committee thought it better that it should adjourn consideration of the case until November. It should be impressed on Mr. Downie that he should be present on that occasion.

APPLICATIONS FOR RESTORATION

The committee rejected applications for restoration from *Louis Aimée Newton* and *Liam O'Shea*.

Points of View

WHAT MAKES THE PATIENT BETTER?

AINSLIE MEARES
M.D., B.Agr.Sc. Melb., D.P.M.
OF MELBOURNE, AUSTRALIA

I AM very often perplexed because I cannot find any satisfactory reason why the patient has got better. When a patient does not get better, it is easy enough for me to assume that my skill as a psychiatrist is wanting. But what of the patient who genuinely recovers from his nervous or psychosomatic illness after two or three visits, when he has not been given any direct suggestions of improvement, and he has no real insight into the mechanisms which produced his illness? Conversation with colleagues leads me to believe that this experience is not uncommon among both general practitioners and psychiatrists. We seldom take much notice of it, save that we somehow have the feeling of having handled the patient well. Is there some other basic factor in psychotherapy beyond the mechanisms of suggestion and insight?

In the first place, we know that the self-adjusting mechanisms of the mind restore homœostasis in the minor nervous upsets of everyday living. In a similar way, it is not uncommon for a patient to recover spontaneously from a nervous illness as a result of some kind of intrapsychic readjustment while his environment remains substantially unchanged. Other cases remit as a result of a lessening of external stress, or because of some therapeutic experience in the patient's life situation. These mechanisms cannot account for the unexpected relief of symptoms in the cases to which I refer, because many of these patients had been ill for some time, and there is no reason why spontaneous remission should so frequently coincide with their attending the doctor.

Is it suggestion? I very well know that the simple fact of the patient coming to the doctor carries with it a powerful suggestive effect for the relief of symptoms. But these patients have all been subject to the suggestive effect of attending other doctors without improvement; and they have usually been exposed to the additional suggestive effect of various tranquillising drugs; and many have already been given direct verbal suggestion of improvement by the referring physician. I do not see how indirect suggestion can account for the improvement of these cases.

Could it be that the patient gains greater insight from a few talks than I think he does? If by insight we mean some kind of rational logical understanding of the psychodynamics which led to his illness, I am sure that this is not so. In fact, many of these strange remissions have been in patients with whom I have spoken least.

We know that nervous symptoms often subside after the cathartic effect of abreaction. But this does not apply to my discussion because these unaccountable improvements often follow particularly quiet interviews in which very little is said by either party. It is not a disguised religious experience, because many of these patients have already sought the help of their church. Nor can the idea of reliving the traumatic event in the therapeutic setting be invoked. It seems that the patient simply gets well in the absence of any clear rational explanation in terms of current psychological teaching.

* * *

This has brought me to examine the psychodynamics of the recovery of patients whom I have successfully treated by either suggestion or " insight " psychotherapy. I often use suggestive hypnosis with patients whose symptoms are not maintained by active conflict. I find that I have often written back to the referring physician saying that the patient was relieved of his symptoms by so many sessions of hypnotic suggestion. Many of these patients have done very well and are known to have remained well for some years. The disquieting matter is that, on further thought, I really doubt if suggestion by itself was always the effective psychological mechanism. These doubts arise from the fact that many of those patients who did best received very little verbal suggestion indeed. This, of course, takes no account of the effect of indirect non-verbal suggestion; but if suggestion is the effective mechanism, it seems strange that the non-verbal form should be so much more effective than the verbal. In many successful sessions little was said, but there was always a very good positive relationship with the patient.

Many patients treated with insight psychotherapy have done well; but in retrospect two features stand out. Several patients who appeared to have very complete insight into the psychodynamics of their illness still retained their symptoms, but in each case my deeper relationship with the patient was not satisfactory. On the other hand, several patients receiving insight therapy made apparently complete recoveries; but on looking back it seems that their degree of insight could not logically account for their recovery. With each of these patients I had a satisfactory deeper understanding. Perhaps I can explain this more clearly by an example:

A few years ago I reported the case-history of a schizophrenic girl of very poor prognosis, who finally recovered completely from her psychosis after psychotherapy around spontaneously produced symbolic paintings.[1] The sequence of the paintings shows clearly how she gained insight into her castration complex. This insight was accompanied by remarkable symptomatic improvement. The logical reason for her recovery through this insight was dramatically expressed in the paintings for all to see. But on re-examination of the case, it would seem that insight was more apparent to the observer than it was real to the patient. It seems that in addition to insight some other factor must have been operating. Again with this patient, although she was psychotic, I had a relationship of deep understanding.

* * *

This leads us to another point. It is now fairly widely accepted that some psychiatrists have the ability to give successful psychotherapy to schizophrenics while others have not. This ability is not clearly related either to formal psychiatric training or to knowledge of psychodynamics. It is usually held that such therapists have a high degree of empathy, and work intuitively, and that these characteristics cannot be acquired, or at least are not developed by conventional psychiatric training. However, this in itself is not a really adequate explanation. The intuitive person arrives at a correct conclusion by some process other than logical steps of reasoning. But in these cases there is often remarkably little conscious exchange of ideas. We see this situation in its extreme form when a schizophrenic improves after forming a relationship with some understanding but quite untrained person. Such situations are by no means uncommon, and might lead us to feel that our relation with the patient is the all-important factor, and that the therapeutic effect of contact with the untrained individual is the result of his intuitive ability to make appropriate emotional responses.

I should like to quote one further personal experience: A few months ago I made a trip to Burma, India, Kashmir,

1. Meares, A. The Door of Serenity. London, 1958.

and Nepal, in an attempt to find out something of the control of pain by Yoga. In Katmandu I saw quite a lot of an ancient Yogi who spoke perfect English. This man was half saint, half philosopher. He had an extraordinary calm about him—a deep serenity which I have never seen in any Western person. I talked with him daily for eight days. During this period I myself took on a much greater calm than I normally have, and I also became much more tolerant of frustration. But my own personal life was never even indirectly discussed with the Yogi, nor did he make any emotional response either to me or to the content of our conversation. As a Yogi he practised and achieved non-attachment, which is really a complete absence of affective response to persons, things, or ideas, and therefore I do not think that his influence on me was mediated through the mechanism of the appropriate emotional response.

Few of us talk with Yogis, but it is not altogether uncommon to experience this phenomenon in less degree. Sometimes when talking with a very calm person, one finds that one's own anxiety is lessened.

These observations seem to indicate that some other factor besides suggestion and insight, and their subsidiary mechanisms, operates in the therapeutic situation. It may be that this factor can be resolved into some particular aspect of the physician's relationship with the patient, or more likely this relationship is the milieu which allows this other mechanism to operate.

We have the observed fact that disturbed patients often regain their mental equanimity after vastly different types of psychotherapy. There is not even any close relation between clinical diagnosis and the type of successful psychotherapy. For instance, different patients with anxiety states may lose their symptoms and remain well after simple suggestion, insight psychotherapy, supportive therapy, relationship psychotherapy, simple explanation, or hypnotic suggestion. Although we often like to think so, the actual psychodynamics of the condition do not even provide a really reliable guide in this matter. In other words, many patients who appear to have a deep and complex disorder of the psyche still lose their symptoms after remarkably superficial psychotherapy. I used to believe that all the various approaches and techniques of psychotherapy fell into two great classes—those which helped the patient by increasing repression, and those which helped him by increasing his insight. Thus reassurance, simple suggestion, supportive therapy, relationship therapy, religious therapy, and hypnotic suggestion all seemed to work towards increasing repression. Explanation, abreaction, analytical psychotherapy, psychoanalysis, and hypnoanalysis all seemed to help the patient by giving him greater insight. This classification is neat, and would appear logical enough. But is it really valid? I doubt it. Where do these unexpected remissions fit in? What of the therapeutic effect of the vivid experience of the moment —of existence?

I have a great abhorrence of those who write destructively. That is not my purpose. I am not trying to say that all we have gained is no good. Rather am I trying to say that surely there must be another way of looking at things. I feel that there is some basic mechanism which, so far, eludes us. Is there some other factor in psychotherapy which is beyond our present theoretical constructs, and which operates unbeknown to the therapist?

* * *

PS.—As this is really a very personal communication, perhaps a postscript is not inappropriate:

Some months ago a physician telephoned, asking me to see an acutely distressed and impulsively suicidal young woman. She had been disturbed for some years, and she had made past suicidal attempts. She had had many months of analytical psychotherapy and narcoanalysis, and, more recently, electroconvulsive therapy (E.C.T.). She refused to see any of her former psychiatrists.

"Can't you get her into hospital quickly? She will need E.C.T. straight away."

But the disturbed young woman became one of those patients who present this theoretical problem of getting better without adequate logical reason.

It is difficult to write to the referring physician saying that his patient is better, when you are unable to explain what you did for her or why she got well. I dawdled about the letter. A month later the physician telephoned me again:

"I have just seen that patient I sent you. She is really marvellous. She has not been as well as this for three or four years. I believe you fixed her without E.C.T."

"Yes."

"One of the new tranquillisers?"

"No. I told her she need not take any drugs."

"She told you something that she had kept from the other psychiatrists?"

"No. She really told me very little."

"You hypnotised her?"

"No. I could not hypnotise anyone as distressed and hostile as she was."

"What did you talk to her about?"

"Really I hardly talked to her at all."

"This is crazy. I am going to stick to proper medicine. Anyhow, I am glad you fixed her."

Perhaps it is good to laugh at such incidents. But then we often laugh when we are on the verge of some truth that we do not quite understand.

Occasional Survey

COMFORT AND EFFICIENCY IN THE TROPICS

TWENTY-FIVE years ago *The Lancet* reflected on the loss of efficiency suffered by white inhabitants of the tropics.[1] Since then improved treatment and control of infectious diseases have shown climatic heat to be a relatively uncommon cause of morbidity and—so it would seem to the casual observer—of impaired efficiency. Studies on healthy young men have revealed, however, that above certain levels of surrounding temperature and humidity both physical and mental performance deteriorate: a man who is uncomfortably hot is measurably less efficient at his job. Much of the work which has helped to prove this was undertaken under the ægis of the Royal Naval Personnel Research Committee of the Medical Research Council; and a collective account, based on reports submitted up to 1953 to the committee by associated workers in London and at the Royal Naval Tropical Research Unit in Singapore, has been compiled admirably by Dr. R. K. Macpherson.[2]

Broadly speaking, environmental heat stress can be assessed by two methods. In both, the air temperature and humidity, radiant heat, and air movement are all measured and recorded. At the same time in the first, or subjective, method individuals exposed to the climate are asked to say how they feel—for example, whether they are comfortable or too hot—whereas in the second, or objective, method their sweat loss or body temperature is measured. The first method was developed in the laboratories of the American Society of Heating and Ventilating Engineers by the late Prof. C. P. Yaglou (then Yaglogou)[3]; and he and his colleagues devised thereby a scale on which simultaneous readings of temperature, humidity,

1. *Lancet*, 1936, i, 379.
2. Physiological Responses to Hot Environments: *Spec. Rep. Ser. med. Res. Coun., Lond.* 1960, no. 298. 35*s*.
3. Yaglogou, C. P., Miller, W. E. *J. Amer. Soc. Heat. Vent. Engrs*, 1924, 30, 515.

and air speed may be expressed arbitrarily as so many degrees of effective temperature (E.T.). In London Dr. T. Bedford, working along this line, modified the scale to account when necessary for radiant heat.[4]

The Royal Naval and Medical Research Council workers began by examining in London the general applicability of the effective temperature scale. They found that it underestimated the deleterious effect of low air-speeds in hot, humid conditions; and that, whereas it implied continuous improvement with rising air-speeds, there actually comes a point (when the air temperature is greater than 100°F [37·8°C] and the air speed is faster than 300 ft. a minute) when further increase in the rate of air-flow increases the heat stress on the body. These findings were confirmed later by the Singapore workers. Another conclusion in London, not confirmed in Singapore, was that the scale over-emphasised the effects of wet-bulb, and underestimated the effect of dry-bulb temperatures. The E.T. scale is based essentially on the subjection factor of comfort; and its inadequacy when applied to men performing hard work in severely hot and humid environments was not unexpected. It remains a useful and convenient method of assessing comfort (or discomfort) in the middle range of environmental heat stress.

The shortcomings of the E.T. scale turned the attention of the London group to the second, or objective, method of assessing heat stress. They had observed that, when energy expenditure was constant, sweat loss was closely related to environmental conditions; and this led them to develop a new scale, also empirical, which they called the predicted four-hour sweat-rate (P4SR).

For this it is necessary to record the globe or dry-bulb temperature (whichever is the greater), the wet-bulb temperature, and the air speed of the environment, and to take account of the energy expenditure and type of clothing worn. It is then possible by means of a nomogram to predict with fair accuracy the average evaporative loss of fluid (in terms of weight loss in a unit of time [sweat-rate]) in healthy acclimatised young men during four consecutive hours if conditions remained stable at the measured levels. A P4SR index of 4·5, implying a loss of 4·5 litres of sweat in four hours, was tentatively suggested as the upper limit of tolerance for fit, acclimatised young men. This index of 4·5 concerns tolerance and not comfort, and it was recognised that before it was reached efficiency would be adversely affected.

A statistical comparison of the E.T. scale and the P4SR has shown that the latter gives more accurate guidance in severely hot environments.[5]

Yet another index, devised by Yaglou, is called the wet-bulb, globe-thermometer (W.B.G.T.) index. This is for use out of doors, and is obtained from the sum of: 0·7 of the wet-bulb reading in the sun and wind, 0·2 of the reading of the globe thermometer similarly exposed, and 0·1 of the dry-bulb temperature in the shade. It has been applied with success to the prevention of heat casualties among recruits at training-centres for the U.S. Armed Forces.[6]

The value of the P4SR scale was examined by the Singapore workers. Like their London colleagues, they made their observations in controlled laboratory conditions; but whereas in London the subjects returned between heat exposures to a cool and recuperative climate, in Singapore they were resident in the tropics. In Singapore the sweat-rates of the subjects were observed to be reduced by water depletion, which in the tropics is an imponderable factor with an obviously dangerous influence on an index which assumes that sweating increases pari passu with heat stress.

Many of the observations in Singapore concerned heat acclimatisation, which has a profound influence on efficiency and on the ability to withstand extremes of heat. Outside the controlled temperatures and standard tasks of hot-room experiments, acclimatisation is a relative phenomenon. On exposure to the same hot-room conditions as their London counterparts had experienced, naval ratings in Singapore showed at first a superior tolerance to heat and therefore some degree of natural acclimatisation; but in the end both groups attained the same degree of " artificial " acclimatisation.

Finally, the useful work carried out in Cambridge by Mackworth [7] on the effects of heat on the performance of a sedentary and semiskilled task, such as morse-code reception, was continued in Singapore. This work clearly showed that efficiency falls when the indoor effective temperature rises above 83°F (approximately 28°C). The activities of the R.N.P.R.C. in respect of heat stress are summarised by Ellis,[8] who was in charge at Singapore.

In knowledge at least, we have come a long way since construction of refrigerated offices in Calcutta suffered the editorial scorn of a London newspaper.[1] The value of air-cooling is still occasionally challenged, mainly because it is expensive but also because of the British tendency to see virtue in roughing it. (In the words of Noel Coward: " Mad dogs and Englishmen go out in the midday sun.") There are sometimes more subtle complications. In the Persian Gulf a few years ago, aboard a merchant ship on which a young man died from heatstroke, the captain was asked to press his employers to provide air-cooling at least for the sick-bay. He replied: " And have all my crew reporting sick just to be *comfortable?* Not likely." Nevertheless, a considerable proportion of the ships which sail east of Suez are now at least partly air-cooled. Their crews have never been so comfortable, but it is likely too that they have never been so efficient.

C. S. LEITHEAD.

4. Bedford, T. *M.R.C. (War) memor.* 1946, no. 17.
5. Smith, F. E. *M.R.C. memor.* 1955, no. 29.
6. Minard, D., Belding, H. S., Kingston, J. R. *J. Amer. med. Ass.* 1957, **165**, 1813.
7. Mackworth, N. H. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1950, no. 268.
8. Ellis, F. P. *Brit. J. industr. Med.* 1960, **17**, 318.

Public Health

Infectious Diseases in England and Wales

Diseases	Week ended May			
	6	13	20	27*
Diphtheria	2	4	3	6
Dysentery	506	458	479	385
Encephalitis:				
Infectious	1	..	2	1
Postinfectious	2	3	2	4
Food-poisoning	183	615	169	236
Measles, excluding rubella	20,456	22,443	24,345	22,345
Meningococcal infection	19	10	12	17
Ophthalmia neonatorum	22	16	26	11
Paratyphoid fever	18	17	10	5
Pneumonia, primary or influenzal	191	195	223	213
Poliomyelitis:				
Paralytic	6	14	11	9
Non-paralytic	3	5	3	13
Puerperal pyrexia	151	158	141	135
Scarlet fever	517	445	448	384
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	454	471	391	364
Meninges and C.N.S.	4	4	5	6
Other	73	81	61	46
Typhoid fever	1	3	1	1
Whooping-cough	723	680	527	451

*Not including late returns.

In England Now

A Running Commentary by Peripatetic Correspondents

ONE of the sillier pieces of literary eyewash is that famous remark about travelling hopefully being better than to arrive. If you want to get somewhere, you want to get there, and that's that. There is no virtue in standing in corridors, changing at Crewe, and otherwise enduring agonies and generally wasting time—the chap who wanted to go on travelling hopefully must have been masochistic. But it must be said that having got there, on foot, by camel, or even by overnight bus, you do feel a satisfying conviction that you have somehow earned it. Not so with air travel these days. The only way to get somewhere by plane and feel you've earned it is to miss the special bus and just catch the thing by taxi, to smuggle diamonds, or to get into Egypt on your wife's expired Israeli passport. Otherwise the whole thing is so darned easy and comfortable that stepping out at New York, apparently 2 hours after you left London (the clocks say so anyway), you feel less exhausted than if you'd taken an afternoon trip to Bognor Regis.

Travelling by air, however, though easy on the muscles, is not without its anxieties. From the moment you step inside the terminal at Victoria the real world (to me anyway, one of the few earth-bound people left) is left behind. True, Pimlico, Chiswick, and Hounslow pass the bus windows, but *differently*. Derealisation is the word. Efficiency, in London anyway, is frankly astonishing. Baggage check, passports, customs, duty-free whisky, follow the green light, and before you know where you are you're settled into a comfortable seat by a sylph-like maiden in beautiful blue. By the time you've found somewhere to stuff your camera, field-glasses, travelling rug, slippers, raincoat, books for the journey (all carried free, unweighed) and your legs, the anxiety begins to mount. The jet engines don't look fixed on too securely. There are dents and scratches in some of the wing panels, where some engineering oaf has been stamping about. Going to be taken out of service after this flight probably, and sold off cheap to a freighting company or turned into saucepans. Confidence is not boosted by a blue and white tract in six languages tucked in front of you called SAFETY LEAFLET which tells you how to sit when the aircraft crashes (bent forward, arms round head), how to inflate life-jacket, and please take stiletto heels off before entering rubber dinghies. You master all this (even less reassured by the comments " In the unlikely event of . . . "), in time to hear it all again over the intercom. and see it demonstrated up front by a blonde. The Captain chooses this moment to announce that owing to " minor technical trouble " the flight will be very slightly delayed. Wing come loose, probably. Mood music by intercom. and glucose sweets brought round would have helped a bit, had one not jolly well known they were *intended* to allay anxiety.

The exhilaration of sheer power behind the thrust at take-off banished fear, but, to a chronic vertiginetic the view straight down is both compelling and horrifying. Best to take it as one of those weird falling dreams that partial insight allows one to enjoy at the time. Indeed, the derealisation intensifies and the dream-like quality grows as the air-currents wobble one gently about, strapped to a snug womb-like, all-enveloping, foam-rubber armchair. Regression is enhanced by the steady flow of duty-free liquor (everything served double). Nor is the real world brought nearer by a peripatetic sheet of cardboard that tells us: " The route is from Shannon to Gander via weather-ships ' J ' and ' C ', and thence via Sydney, Yarmouth, and Boston to New York ". Oh well, I suppose that's one way to get there.

* * *

For a registrar reading during ward-rounds can be frustrating. Magazines may have to be read sideways or upside down, and some of their contents deduced when pages are half-covered. Occasionally a badly placed newspaper can be moved while the chief is examining a patient, or position casually altered to a better vantage point. Unfortunately, it is the chief who decides when it is time to move on to the next patient. Sometimes an article in a very popular newspaper can be resumed at the next bed, but all too often the round ends with much that is of interest only half read, and with the nature of many half-covered illustrations still uncertain. It must be wonderful to be a consultant and read the patients' magazines and newspapers openly, turning them, uncovering them, and even holding up the round when necessary.

* * *

There is no doubt that hospital doctors could learn from the professional football clubs. This is their transfer season, when outstanding players may be moved from town to town or even country to country for very large sums indeed. Economic factors dictate where they shall go.

Now why not apply this method to patients? The scarcity of good clinical material in the big teaching hospitals is well known, while their funds seem to be unlimited. Fascinating cases continue to be admitted to peripheral hospitals, but could well be transferred to the centre—for a suitable consideration to the clinician-in-charge. The effect on the health service would be electrical. In an effort to find the right kind of patient, waiting-lists would drop, turnover would increase, and the level of diagnostic acumen in the periphery would rise rapidly. For the patients transfer would be an honour to which they could scarcely object, and besides it is generally agreed that they exist for the benefit of the doctors.

There may be a snag of course. If the regional boards should get to hear of this they, too, might follow the example of the football clubs. Suppose they opened their own transfer lists —not of patients but of consultants.

* * *

My patient, aged 74, has severe osteoarthritis (one hip-joint is quite obliterated), asthma and emphysema, and syncope attacks. On her way to see a hospital cardiologist, the ambulance driver was most attentive and saw her to a seat in the out-patients' waiting-room.

In due course she undressed, was examined, then told to put on all her clothes again and go upstairs to the pathology laboratory for a blood-test. She climbed a long flight of stairs, walked along a corridor; here only her coat, jacket, and jumper had to be removed and replaced. Retracing her journey she again undressed, was X-rayed, and told to get dressed quickly. Then off again, a long walk to ward 20 to have an E.C.G., clothes off again, but she was told to keep on her knickers. The E.C.G. taken, she again dressed herself and walked down the long corridor (which then seemed miles) to her seat in the out-patient hall, there to await transport.

The physician writes: " There is evidence of a recent postero-septal infarct. She must take things very quietly and I will see her for review in a month." My patient asks whether the National Health Service will supply her with a physical-training instructor to help her to be in better training for her next visit.

* * *

Many of the patients who attend our hospital are seamen and their symptoms are usually related to points on the globe rather than to time. The man with the peptic ulcer first developed indigestion while rounding the Horn and had his first hæmatemesis in the estuary of the River Plate. The tuberculous patient developed a cough shortly after his ship left Sydney and he had a hæmoptysis in the Gulf of Aden. The youngster with rheumatic heart-disease became dyspnœic when his ship was steaming between Yokohama and Hong Kong and his ankles began to swell in the Bay of Bengal. Even functional dyspepsia becomes interesting when it develops in San Francisco Bay or off the coast of Coromandel.

* * *

I have just finished reading some applications for appointment. One chap boldly described himself in uncial as " Horse Physician, Hammersmith Hospital ". Well, we'd better have him. I've often thought our hospital was a bit of an animal house, and he'll get adjusted to life with the lesser quadrupeds.

Letters to the Editor

FIRST THINGS FIRST FOR THE INJURED

SIR,—May I heartily endorse all that you said in your excellent leading article last week.

The prevention and treatment of accidents is one of the major problems facing us today. With regard to prevention there is still far too much apathy in official circles, particularly about road accidents.

In my town there is a number of notorious crossroads; and it is a standing " joke " in the town that *x* people must be killed before the Ministry of Transport will install a " Halt " sign.

As doctors we can do little to prevent accidents, but we can do far more than at present to save the lives of the seriously injured. The organisation of an efficient accident service in a middle-sized town with a population of 25,000–100,000 is not easy, as serious accidents are not frequent enough to justify employing a full-time staff specifically for treating accidents, as in Birmingham.

The first essential is to have a fully equipped accident department in which complete resuscitation, including artificial respiration, can be started within seconds of the patient's arrival. The second essential is to have trained staff ready to act. As I see it, the best way to achieve this in a relatively small community is to have a list of consultants and general practitioners able and willing to come at short notice to the accident department; at least two of them would be summoned at the same time as the ambulance leaves. The essence of this system would be to have as many names on the list as possible, but to include only those conversant with up-to-date resuscitation techniques. There are, for instance, many general practitioners who have had training in anæsthetics.

The advantage of this system would be that there would almost always be someone free to come at short notice, and it would avoid a rota system which is frequently upset by holiday and illness, and by the fact that surgeons and anæsthetists and others may be in the theatre and unable to leave at once.

A final and most important point: with increasing experience I am becoming more and more convinced that a very substantial proportion of accident victims who are " killed " at the roadside do in fact die simply from asphyxia resulting from an obstructed airway after a knockout blow. There is seldom a bystander with sufficient knowledge to maintain a clear airway in an unconscious patient. It is rather as if a deeply anæsthetised patient were thrown at the feet of an interested but untrained crowd. He would almost certainly die. I am convinced that there is a big part to be played by an intensive information campaign, both on television and by local lectures and demonstrations, on how to keep the airway clear in an unconscious patient, and this could be combined with instruction in expired-air respiration. Much prominence has been given recently to expired-air respiration and external cardiac massage; but these measures are seldom necessary provided that the airway can be cleared within 2-3 minutes after a knockout blow.

I do not believe it is an exaggeration to say that if the measures outlined above were to be put into practice the present death-rate could be more than halved.

Eastbourne. P. HEX VENN.

LABELLING OF MEDICINES

SIR,—I write to express my wholehearted agreement with Professor Wilson's letter (May 20), and to join him in deprecating the decision of the Joint Formulary Committee.

For the past five years all prescriptions issued from my chest-clinic sessions have been rubber-stamped: " Please put full name and strength of drugs on container ". This was because so many chemists either did not know the meaning of " *N.P.*", or simply ignored it. Even when the prescription is stamped, I find these instructions are often ignored.

I originally began having drugs labelled because this has so many obvious advantages. Nowadays it is seldom necessary to conceal treatment from the patient, who in any case seldom appreciates the significance of the drugs' names. When drugs are prescribed from an outpatient department, it is always possible that the family practitioner may be called in before an explanatory letter has reached him; or, even if it has, he may have forgotten what was prescribed, or the patient may not see the member of the firm who referred him and this second doctor will not have read the letter. In addition there are all the other possibilities mentioned by Professor Wilson.

It must be most embarrassing to be confronted by a patient rattling a box of unidentifiable pills, demanding a further supply because they have been so effective. Should the patient's card not be available, or the drugs have been prescribed by another doctor, or not noted on the card, the doctor can look extremely foolish.

I have often been astonished by the quantities of unlabelled drugs which are found by the bed or in the cupboard when patients are visited at home. A very great deal of money must be wasted annually in this way. If any patient of mine fails to use all the drugs prescribed, he is asked to return them to the clinic. Because they are clearly labelled they can be reissued to other patients urgently requiring them.

Surely the days of mumbo-jumbo went when so many really potent, expensive, and dangerous drugs were introduced. Clear labelling of drugs could be introduced into all types of practice to the mutual advantage of both doctor and patient, and thereby save time, temper, and a very large sum of money.

The Chest Clinic, Derby. H. MORROW BROWN.

SIR,—The convention of putting " *N.P.* " or " *Nom. Prop.* " on prescriptions either is not understood or is ignored by so many chemists that I had this rubber stamp made, which I apply to all of mine:

REPEAT IF		TIMES REQUIRED
Please supply tablets and proprietary preparations in clearly named, preferably original, containers.		

It has not made much difference.

Kingston upon Thames. CHARLES STEER.

NEEDS AND BEDS

SIR,—Your symposium and editorial promise to shed light on some of the darker corners of the health service. The myth that the hospital bed has inherent healing powers is overdue for exploding, but resistance from various pressure groups is likely to prove formidable.

Areas like Burnley and Oldham would seem tailor-made for a planned investigation into the effects on family life of keeping chronic psychotics and other permanent invalids in their own homes. Such an investigation should be made by an independent team of investigators. The views and needs of relatives, of busy and impatient family doctors, and of health visitors and other welfare workers must be considered, to say nothing of the views and needs of the patients themselves. It may show that the psychotics find hospital treatment outside their home areas. The danger of their being totally neglected in the interests of arresting statistics is also a remote possibility.

In pleading for psychiatric units in general hospitals, it is scarcely justifiable to worry too much about the future

of the county mental hospitals. Their isolation can hardly be more extreme than it already is and their concealed decay has been rapidly revealing itself over the past decade or so. When they are relieved of the mounting pressure of admissions and given an opportunity of decongesting themselves, they can revert to the glories they enjoyed in the Augustan age of Connolly and his inspired colleagues. Their medical staff, at every level from senior house-officer upwards, should spend at least half of their working week at outpatient clinics. However junior or inexperienced a mental-hospital doctor is, he can at least do as much for the psychiatrically ill as the busy general practitioner who is often handicapped by his failure to get early appointments for his patients at psychiatric outpatient clinics. The danger of the mental hospital becoming a place for the sheltered employment of some doctors would then be avoided.

Liverpool, 8. G. P. EGAN.

THE FIBERSCOPE

SIR,—The development of the fiberscope is a notable advance in the field of endoscopy. The ability to transmit a perfectly clear image through a completely flexible tube will provide many opportunities for the internal examination of organs hitherto inaccessible. Dr. Hirschowitz is to be congratulated on his ingenuity and perseverance in adapting the glass-fibre optical transmission system for use in a gastroscopy.

Our own experience of this instrument is at the moment limited to forty cases; and it would be premature to express a final opinion on it. There is no doubt that the instrument is easier to pass and more comfortable for the patient than the conventional semiflexible gastroscopes at present in use; and the fact that the neck remains flexed throughout the examination avoids the risk of damage to the posterior pharyngeal wall from pressure between the shaft of the instrument and any osteophytes on the anterior aspects of the cervical spine. The quality of the view obtained is excellent, but the flexibility of the instrument which makes it so acceptable also makes it more difficult to control the position of its head, and in particular to inspect the posterior wall of the stomach.

We cannot subscribe to the view that the instrument passes easily into the duodenum, for the only two occasions on which we have been able to inspect this organ have been when the fiberscope has been threaded into it by a surgeon at laparotomy; and we were unable to see anything clearly as the mucosa was too close to the optic. Even with radiological screening we have found it impossible to pass the instrument through the pylorus.

In our present view, therefore, this instrument opens up very great opportunities for the future but has not yet superseded the more conventional gastroscopes.

Central Middlesex Hospital, London, N.W.10. F. AVERY JONES
T. D. KELLOCK.

SIR,—The novelty value, and the enthusiastic reports published recently in your columns and elsewhere, of the fiberscope endoscope, suggests that a note of caution may be desirable. The actual image quality obtainable from a fiberscope is inescapably limited by the number of fibres per unit area of its cross-section.

The smaller the fibre, the greater this number, and hence the better the definition; but even so it can never, in a small bundle such as is needed for the duodenum (or, even smaller, for the kidney pelvis), provide a sharp image. Moreover, the smaller the fibre, the lower its efficiency in light-passing capacity; these two restrictions must be adjusted so as to provide a useful working compromise. The outcome is a range of instruments which can provide information not available in any other way: but the image they yield is, and always must be, unsharp compared with the image provided by normal optical endoscopes. Since enormous improvements are now being made to these also, it would be wrong to suggest that the fully flexible fiberscope can replace the rigid or semiflexible endoscopes for those examinations where their use is already fully proven. The fiberscope is to be welcomed as an additional clinical instrument of great potential value in hitherto inaccessible regions once the early technical difficulties in its manufacture have been fully overcome.

London, W.1. BRIAN STANFORD.

DRINKING-WATER

SIR,—In your annotation (June 3) you write of "the enthusiasm and excitement of a Balkan village which has exchanged ancient wells and cisterns for clean water from the tap". This phenomenon has recently occurred in a Sussex village about 60 miles from London. The cottagers on the outskirts still drink water from "ancient wells", never—at least in the past 16 years—officially inspected or tested.

Hove, Sussex. G. M. WAUCHOPE.

NEW CONCEPT OF CAPILLARY CIRCULATION IN BONE

SIR,—In their paper (May 20), Dr. Brookes and his coworkers quite rightly state that the results of their work "suggest that a reorientation of clinical thought is necessary". Because of the important clinical implications of their view that blood flows centrifugally through the cortex from medullary bone and only flows centripetally in diseased states such as peripheral vascular occlusive disease, their results need examining with some care.

Brookes et al. wrote ". . . the blood in the capillaries [of the cortex] cannot go both ways, centripetally from the surface and centrifugally from the marrow". This statement in itself is rather puzzling. The blood cannot go both ways in the same set of capillaries at the same time, but surely there is no reason why it should not go centrifugally through one set of capillaries and centripetally through a different set, as has been described in the heart, for example. The statement is also puzzling because they later say ". . . compensation [in ischæmic conditions] is achieved in part by a centripetal flow into the cortex from the external soft tissues".

If one accepts their first statement, then the latter either means that in these diseased states the flow in the cortical capillaries is actually reversed or that new vessels appear with a centripetal flow.

We have investigated the blood-flow in bone-marrow and its overlying muscle in the anæsthetised cat by a heated thermocouple technique. Simultaneous recordings were made of intramedullary pressure and systemic arterial blood-pressure. Our experiments have shown that when the limb is exercised or its venous return is occluded, the medullary pressure and blood-flow are considerably increased. This suggested to us that blood was shunted from muscle into bone. In an attempt to confirm this suggestion we tied a very tight ligature round the mid-thigh, occluding all soft-tissue blood-flow below the ligature. Radio-opaque material was then injected into the anterior tibial artery below the ligature and, a few seconds later, X-rays showed a distinct vessel in the femoral medullary cavity extending above the ligature. There was also filling of the femoral vein in the femoral triangle. In our view this experiment, which has been repeated many times, provides convincing confirmation of our view derived from the blood-flow studies, that, at least in the cat, blood passes from the soft tissues into the bone—i.e., centripetally.

Brookes et al. state: "The plan of cortical vascularisation . . . shows that the blood-flow may be reversed if the *vis a tergo* of medullary arterial pressure should fall." It is not

just pedantic to comment that their plan, if correct, shows that such a reversal of flow is anatomically possible, but a plan does not, and cannot, show that it ever occurs in fact. Our experimental evidence strongly suggests that increased centripetal flow occurs not through reversal of flow in centrifugal vessels but through increased flow in existing centripetal vessels.

Clinical Research Wing, Institute of Orthopædics, Stanmore, Middlesex.
A. McPHERSON
N. E. SHAW.

TRIPLOID CELLS IN A HUMAN EMBRYO

SIR,—Since the finding of triploid cells in a human embryo by Penrose and Delhanty,[1] we have observed a further instance of the same phenomenon in an embryo which miscarried on April 8, 9 weeks after the date of the last menstrual period (Feb. 2, 1961).

This was the first pregnancy of the mother (aged 21) who was admitted to hospital after one day of vaginal bleeding.

Fig. 1.

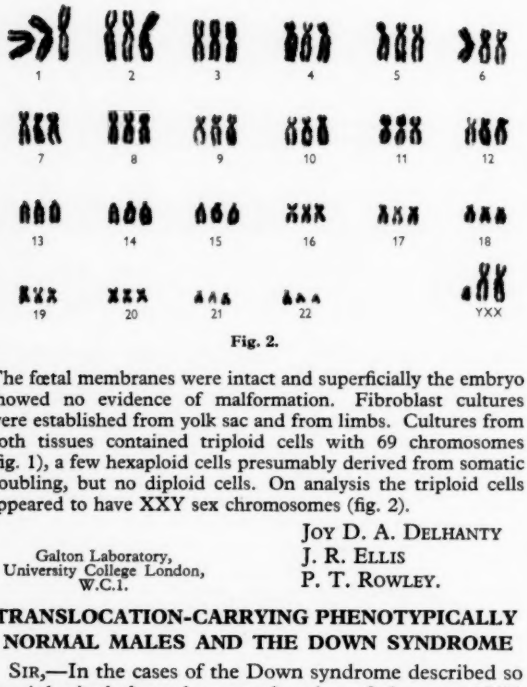

Fig. 2.

The fœtal membranes were intact and superficially the embryo showed no evidence of malformation. Fibroblast cultures were established from yolk sac and from limbs. Cultures from both tissues contained triploid cells with 69 chromosomes (fig. 1), a few hexaploid cells presumably derived from somatic doubling, but no diploid cells. On analysis the triploid cells appeared to have XXY sex chromosomes (fig. 2).

Galton Laboratory, University College London, W.C.1.
JOY D. A. DELHANTY
J. R. ELLIS
P. T. ROWLEY.

TRANSLOCATION-CARRYING PHENOTYPICALLY NORMAL MALES AND THE DOWN SYNDROME

SIR,—In the cases of the Down syndrome described so far, inherited through a translocation of the type 15/21 (Denver nomenclature),[2–4] the anomaly has been passed on by phenotypically normal women. As far as we know, no case in which the syndrome has been transferred via a phenotypically normal man has been reported.

We have recently observed a type 15/21 translocation in a phenotypically normal mother and 2 of her children—1 a girl with the Down syndrome, and the other a phenotypically normal boy aged six years. These children had had a brother with the Down anomaly who had died. A full account of this family will be published shortly.[5]

In another family the mother, since dead, had had 2 children undoubtedly affected with the Down syndrome, and another child who died when a week old who almost certainly was too; in addition, the mother had 5 spontaneous abortions.

The only child still alive, who has typical signs of the Down syndrome, had 46 chromosomes in blood-cells cultured by the method of Hungerford et al.[6] His father had 45 chromosomes. Both these males showed translocation of the type earlier observed in 2 isolated cases of the Down syndrome.[2 7] The healthy father lacked two small acrocentric chromosomes, and had instead an extra chromosome of type 19–20, though this seemed to be slightly larger than usual. The son lacked one small acrocentric chromosome and had the same extra chromosome as his father. These cases will be fully described elsewhere.

Thus, two different types of translocation were observed in 2 phenotypically healthy males, 1 of whom had not reached puberty, and the other had been the father of at least 2 children with the Down syndrome.

Institutes of Social Medicine and Histology, and Department of Pædiatrics, University of Gothenburg, Sweden.
H. FORSSMAN
O. LEHMANN.

DELAY IN PUBLICATION

SIR,—In my letter of May 6 I suggested that delays in publication in the specialised British journals are one reason why British and other investigators are tending more to publish in American journals where in general the publication delay is shorter. Dr. Shirley Smith (May 20) writes that " this statement is at variance with the experience of my journal " and quotes figures which show that for the *British Heart Journal* there has been over the past eight years an overall increase in the number of articles published from the Commonwealth, Europe, and the United States, of from 12% to 30½% of total contributions. But as isolated observations I wonder how meaningful these figures are without knowledge of the rate of increased output from these areas in what, after all, has been a most productive eight years of medical writing, or of the increase in the number of articles by foreign investigators published in corresponding American journals and without considering standards.

What I attempted to draw attention to as one factor was the unduly long waiting period which in some journals elapses between the acceptance of a *final* copy and publication—a delay which is unrelated to major copy editing and is indicated in most journals by the date quoted on which the final copy is received. I don't really feel that Dr. Shirley Smith's statement, " I will never allow the character and worth of the *British Heart Journal* to be sacrificed in the interest of rush publication " to be relevant in this connection.

Finally I do apologise for not recording in my letter the recent change in editorial policy of the *British Heart Journal*, which over the past six months has reduced this delay. For this my excuse is that the facts as presented, referring to the *British Heart Journal*, amongst others,

1. Penrose, L. S., Delhanty, J. D. A. *Lancet*, June 10, 1961, p. 1261.
2. Penrose, L. S., Ellis, J. R., Delhanty, J. D. A. *ibid.* 1960, ii, 409.
3. Carter, C. O., Hamerton, J. L., Polani, P. E., Gunalp, A., Weller, S. D. V. *ibid.* p. 678.
4. Buckton, K. E., Harnden, D. G., Baikie, A. G., Woods, G. E. *ibid.* Jan. 21, 1961, p. 171.
5. Lehmann, O., Forssman, H. *Acta pædiat., Stockh.* 1961 (in the press).
6. Hungerford, D. A., Donelly, A. J., Nowell, P. C., Beck, S. *Amer. J. hum. Genet.* 1959, **11**, 215.
7. Fraccaro, M., Kaijser, K., Lindsten, J. *Lancet*, 1960, i, 724.

were correct at the time my letter was written and submitted last November. That these figures are now out of date for the *British Heart Journal* is attributable to a delay, albeit unavoidable, in publication !

San Francisco, U.S.A. D. E. L. WILCKEN.

*** We add our own apologies.—ED. L.

MEDICAL EMIGRATION

SIR,—In view of Dr. R. H. Davison's article in your issue of May 20, and the leading article in *The Times* of May 20, the following information may interest your readers. Between July 1, 1955, and June 30, 1960, 11,000 assisted British migrants and 19,000 alien migrants arrived in Western Australia. During this period about 150 doctors qualified in the British Isles registered in the State. British migrants who paid their own fares are not included in this total, and the alien migrant figure includes visitors.

It is unlikely that more than a few doctors would come here for educational reasons during this period, and study of the State Register shows that the great majority are still in practice in this State. As it is necessary to re-register each year in Australia, it should not be difficult to discover the overall picture of medical migration to this country from careful study of the State Registers.

School of Medicine,
University of Western Australia,
Perth. J. D. MARTIN.

CHLORHEXIDINE AND *Proteus rettgeri* INFECTION

SIR,—We agree with Dr. Lubsen and his colleagues (April 29) that chlorhexidine is less active against proteus, especially *Pr. rettgeri*, than against most other urinary pathogens. This may be related to the increase of proteus infections which they have observed. But we suggest that their experience is an indication for reviewing the methods of using chlorhexidine and not for abandoning it.

No disinfectant is perfect. One of the shortcomings of chlorhexidine is its relatively slow action against proteus. But its action can be enhanced by mixing it with other agents. The finding that mercuric oxycyanide (itself a poor disinfectant) increased the bactericidal action of chlorhexidine against a variety of bacteria, including the few proteus strains which were tested, led us to recommend a mixed aqueous solution of chlorhexidine 1/5000 and mercuric oxycyanide 1/2000 for disinfecting non-boilable cystoscopes.[1] Subsequently chlorhexidine 1/200 in 70% alcohol was found more convenient.[2] Both methods have proved reliable in practice.

Chlorhexidine is partly inhibited by organic matter (another shortcoming common to many disinfectants). Its bactericidal action in broth is therefore not a good indication of its value in disinfecting cystoscopes, which should first be rinsed in water.

No disinfectant by itself can be relied on to prevent urinary infection after prostatectomy. An integrated scheme of precautions is necessary, as Dr. Stewart and his colleagues point out (May 13). The value of a disinfectant can best be judged by the results of such a scheme in which it is included. In the system introduced in Bristol in November, 1957, chlorhexidine is the principal disinfectant and is used in conjunction with aseptic drainage and irrigation of the bladder. Postoperative urinary infection fell from 83% to 6%.[3] Moreover, we have not observed any increase of proteus in the few infections which still occur, and the incidence of *Pr. rettgeri* has actually diminished. Of 54 unselected proteus strains isolated before November, 1957, 21 (39%) were *Pr. rettgeri*, compared with 1 (3%) of 32 strains examined recently.

1. Miller, A., Gillespie, W. A., Linton, K. B., Mitchell, J. P., Slade, N. *Lancet*, 1958, ii. 608.
2. Miller, A., Gillespie, W. A., Linton, K. B., Mitchell, J. P., Slade, N. *ibid.* 1960, i, 310.
3. Gillespie, W. A., Linton, K. B., Miller, A., Slade, N. *J. clin. Path.* 1960, **13**, 187.

These results, and those obtained by Beeuwkes and de Vries [4] and by Paterson et al.,[5] show chlorhexidine to be a valuable disinfectant in urology and gynæcology. It certainly should not be abandoned until something better is available and has been proved by thorough clinical trial.

W. A. GILLESPIE
K. B. LINTON
A. MILLER
J. P. MITCHELL
Bristol Royal Infirmary,
and
Southmead Hospital, Bristol. N. SLADE.

THE INCIDENCE AND CYTOLOGY OF DIFFERENT MYELOMA TYPES

SIR,—The preliminary communication from Waldenström, Paraskevas, and Heremans, drawing attention to the difference in age-incidence of their "γ_{1A}-globulin" type myeloma from the γ myeloma, prompts me to draw attention to fig. 7 of my article [6] in *The Lancet*, an article to which they refer.

This shows clearly that in our series the average age-incidence of patients showing an excess of β-globulin (probably the equivalent of the "γ_{1A}-globulin" of Waldenström and his colleagues) is significantly lower than the age of patients showing excess of γ-globulin. Indeed, of the β myelomata only four out of twenty-one were over 60 and nine were under 45. The general trend, therefore, seems to be in line with the Malmö findings.

Chemical Pathology Department,
St. George's Hospital Medical School,
London, S.W.1. NICHOLAS H. MARTIN.

AMITRIPTYLINE IN DEPRESSION

SIR,—Previous correspondence in your columns, on the difficulties and uncertainties surrounding the administration of the large and increasing numbers of psychotropic drugs, prompts me to report on amitriptyline hydrochloride (' Tryptizol '), a new antidepressant drug recently released to hospitals, which resembles imipramine hydrochloride (' Tofranil ') in its structure and action.

These are the results of a preliminary uncontrolled study of the action, side-effects, and complications of the drug in 74 patients with depression. 49 women and 25 men were treated. Their ages ranged from 18 to 73 years, and the specific diagnoses were: endogenous depression (50), involutional depression (6), reactive depression (18). No schizophrenics were included. 22 depressed manic-depressives (44%), 5 (83%) of the involutional depressives, and 6 (33%) of the reactive depressives were definitely improved: symptoms of depression disappeared completely, and the patient resumed his normal activities. 11 patients who definitely improved had failed to respond satisfactorily to previous electroconvulsive therapy. Besides its antidepressive action amitriptyline has a strong sedative effect which relieves depressive insomnia and agitation.

An effective dose is 50 mg. three times a day by mouth, but it is probably advisable to start with a dose of 25 mg. t.d.s. for four or five days to reduce the side-effects. Depressive symptoms are not usually relieved until ten to fourteen days have passed. Many patients notice no side-effects, while others (mainly the reactive depressives) complain particularly of drowsiness, which led 10% of them to abandon the drug. This symptom abates rapidly if the patient can be persuaded to continue treatment. Dryness of the mouth is common, constipation and excessive perspiration less frequent. Blurring of vision, heartburn, and difficulty in micturition are rare complications. No hypotensive effects were observed, but giving more than 25 mg. t.d.s. to elderly patients is not recommended.

4. Beeuwkes, H., de Vries, H. R. *Lancet*, 1956, ii, 913.
5. Paterson, M. L., Barr, W., Macdonald, S. *J. Obst. Gynæc. Brit. Commonw.* 1960, **67**, 394.
6. *Lancet*, Feb. 4, 1961, p. 237.

I noted no toxic effects on liver or blood; and other workers have not reported any.

The other main complication is related to the potent antidepressive action of amitriptyline. In 4 of the 74 patients various degrees of hypomania developed. Hence all patients treated with 150 mg. daily should be carefully observed.

Some workers believe that monoamine-oxidase inhibitors are potentiated by amitriptyline, and they have recommended that monoamine-oxidase inhibitors should be discontinued for some weeks before starting to give amitriptyline. My study gave no support for this view.

At present I would merely suggest that amitriptyline is a new and effective means of treating some forms of depression. It has limitations and disadvantages, but, being both potent and apparently non-toxic, can undoubtedly benefit some patients not responding to other forms of treatment.

Netherne and Fairdene Hospitals, Coulsdon, Surrey. DOUGLAS BENNETT.

TREATMENT OF FRIGIDITY

SIR,—I entirely agree with Dr. Abraham's contention (May 27) that many cases are extremely difficult to treat.

It is essential to rule out the possibility that frigidity is related to "variations" in sexual technique, which may amount to perversions on the part of the husband. Many women will not mention these out of feelings of loyalty; it may therefore be necessary to explore under thiopentone or ether to discover them. If no such evidence is found, before suggesting deep psychotherapy I believe superficial psychotherapy, associated with an aphrodisiac, is well worth trying. I usually give 'Potensan', containing yohimbin hydrochloride, which I have found of value in many cases.

Herrison Hospital, Dorchester, Dorset. E. S. FOOTE.

NEUROBLASTOMA AND CATECHOLAMINE EXCRETION

SIR,—We were happy to read that Bell and Steward (May 13) have obtained data confirmatory of our studies [1 2] by finding abnormal variations in the urinary excretion of the catecholamines and their metabolites in 3 patients with neuroblastoma. These findings emphasise that it is important to measure as many of the precursors and metabolites of noradrenaline as possible when evaluating these cases.

We have now been able to study 16 children with neuroblastoma.

12 had striking increases in the urinary excretion of one or more of the following compounds: dopamine, noradrenaline, 3-methoxy-4-hydroxy mandelic acid (V.M.A.), or normetanephrine-metanephrine. The other 4 (including the one previously reported [1]) have had no significant increase in the urinary excretion of these substances. Several possible explanations come to mind: (*a*) there was no catecholamine production by the tumour; (*b*) the turnover-rate for catecholamines in the tumour was so slow that urinary excretion of these substances was not increased; (*c*) the biosynthetic pathway was altered before the stage represented by dopamine was reached.

In accord with the observations of Bell and Steward, we have found no measurable abnormalities in catecholamine metabolism in 9 patients with a variety of tumours of non-neural-crest origin and in 4 children who have apparent cure of their neuroblastoma following surgery, radiation, and/or chemotherapy. These findings support the concept that elevated excretion of the catecholamines and their metabolites indicates the existence of a functioning tumour of neural-crest origin. However, in some instances, a neuroblastoma may be present even though the urinary excretions of dopamine, noradrenaline, V.M.A., and normetanephrine-metanephrine are normal.

Department of Pediatrics, State University of New York, Upstate Medical Center, Syracuse 10, New York. MARY L. VOORHESS LYTT I. GARDNER.

1. Voorhess, M. L., Gardner, L. I. *J. clin. Endocrin.* 1961, **21**, 321.
2. Voorhess, M. L., Gardner, L. I. (abstract) *Clin. Res.* 1961, **9**, 191.

NOT FOR SALE

SIR,—If you call a man a knave, innocent members of the same group are bound to protest. Dr. Dunlevy's strictures on consultant practice (April 1) may not be universally applicable, but there is no doubt that they are true in some places.

Having worked in a number of hospitals in different parts of England, I recall one where "queue-jumping" by private patients occurred regularly. As one might expect, and as Dr. Seale remarks (April 15), the hospital with most abuses was the one with the longest waiting-list. When "cold cases" may wait six months to be admitted to a medical ward, the incentive to put private cases in at the head of the list becomes overwhelming.

Thus, inadequacy of the health service can lead to abuse, and abuses could lead to breakdown of the service, or to Government action against private practice. Hospital improvements are required as well as moral integrity.

Winnipeg, Manitoba, Canada. MICHAEL J. D. NEWMAN.

REVERSIBLE INBORN ERRORS OF METABOLISM

SIR,—Dr. Stanbury in his letter (May 6) takes exception to our reports [1–5] describing an at any rate temporary reversal of an inborn error of metabolism. He feels that the evidence presented by us is inadequate to cast a doubt on the universal validity of the concept of the permanence and irreversibility of these errors.

We found that the short-term (8–10 days) administration of unphysiologically large doses of thyroid substances (90 mg. triiodothyroacetic acid or equivalent doses of desiccated thyroid) produced euthyroidism in three sibs with sporadic goitrous cretinism, and more or less complete regression of the goitres, with evidence of normal function or even hyperactivity of the thyroid for long periods—between 6 and 12 months in two patients, 23 months so far in the third.

Dr. Stanbury suggests that the basic defect in our patients was actually a lack of deiodinase leading to chronic and progressive loss of iodine by the escape of partially iodinated aminoacids (iodotyrosines) into the urine. In such circumstances short remissions were indeed maintained after the withdrawal of substitution therapy or during the administration of iodide, and since the enzymatic defect remained complete and unaltered, they were ascribed to repletion of the organism's deficient iodine stores. [6 7]

We claimed, on the other hand, that the primary disorder in our patients was an inability of the thyroid to hold inorganic iodide and convert it into organic iodine. [8 9] Potassium thiocyanate, though administered to only 1 patient, produced an unequivocal iodine discharge from the gland; this fact is certainly in favour of our hypothesis.[5] But the nature of the enzymatic defect is, in our view, of no importance to the problem in hand. Whatever the basic mechanism at fault, the crucial fact remains that the transient administration of

1. Zondek, H., Leszynsky, H. E., Zondek, G. W. *Acta endocr., Copenhagen*, 1958, **29**, 47.
2. Zondek, H., Leszynsky, H. E., Zondek, G. W. *Brit. med. J.* 1959, i, 340.
3. Zondek, H., Leszynsky, H. E., Zondek, G. W. *Arch. intern. Med.* 1960, **106**, 15.
4. Zondek, H., Leszynsky, H. E., Stein, J. A. *Nature, Lond.* 1960, **187**, 515.
5. Zondek, H., Leszynsky, H. E., Zondek, G. W., Stein, J. A., Guttmann, S. *Brit. med. J.* 1961, **1**, 97.
6. Choufoer, J. C., Kassenaar, A. A. H., Querido, A. *J. clin. Endocrin.* 1960, **20**, 983.
7. Querido, A., Choufoer, J. C. *Proc. int. Congr. intern. Med.* 1960, p. 134.
8. Stanbury, J. B., Hedge, A. N. *J. clin. Endocrin.* 1950, **10**, 1471.
9. Stanbury, J. B., Ohela, K., Pitt-Rivers, R. *ibid.* 1955, **15**, 54.

such short-lived thyroid substances as triiodothyroacetic acid resulted in euthyroidism, both clinical and functional, for periods of up to almost two years so far.[5]

Does Dr. Stanbury really believe that 9 days' thyroid therapy would have sufficed to restore normal thyroid function for so long by repletion of iodine stores? We still feel justified in claiming that the administration of the end-product of thyroid secretion induced a trigger mechanism which removed the basic defect in some as yet unexplained way, possibly by activating an enzyme inactive till then. We are confident that, had Dr. Stanbury focused his attention on the time-factor involved, he would hardly have correlated the lengthy effect of short-term therapy observed by us with the relatively short-lived effect of protracted therapy observed in dehalogenase defects. If so, why not call a spade a spade, and term the phenomenon we observed a " reversibility of an inborn error of metabolism "?

HERMAN ZONDEK
Department of Medicine, Biccur Cholim Hospital, Jerusalem, Israel. HANNAH E. LESZYNSKY
GERDA W. ZONDEK.
Radium Institute, Rothschild Hadassah, University Hospital, Jerusalem. JOSEPH A. STEIN.

AN ADVERTISEMENT

SIR,—Dr. Elmes (May 13) rightly complains of a proprietary drug containing, among other components, small amounts of prednisone.

Some pharmaceutical firms produce all kinds of steroid combinations: aspirin, aminophylline, amidopyrine, and phenylbutazone, for example, have been used in this way. As a rule, the dose of corticosteroid is much too small for effective maintenance, yet it is not certain that these continued small doses are harmless.

It looks as though the makers' aim is to relieve symptoms by an effective dose of an analgesic-antirheumatic drug but to disguise the reason for this success by including an ineffective dose of steroid.

The preparations may be cheaper than an effective dose of steroid, and they may also satisfy the industry's urge to produce " newer and better " drugs at the rate of 700 per year, but there is no good reason for prescribing them.

Berlin. H. HERXHEIMER.

DRUGS USED IN THE TREATMENT OF OBESITY

SIR,—I am prompted by Dr. Elmes' letter (May 13) to draw attention to the two constituents of 'Filon' (each tablet of which contains 30 mg. of phenmetrazine theoclate and 20 mg. of phenbutrazate hydrochloride) and their close chemical relationship to another anti-obesity agent phenmetrazine hydrochloride ('Preludin').

Phenmetrazine theoclate is 3-methyl-2-phenylmorpholino-8-chloro-theophyllinate which differs from preludin only in that it is the 8-chloro-theophyllinate salt of the base, while preludin is the hydrochloride. The approved name, phenmetrazine, appears on the package but not in the manufacturers' literature. I think it should be stated in the literature, for, as your readers will be aware, phenmetrazine hydrochloride can produce side-effects and addiction.[1–3] The manufacturers of filon say that the 8-chlorotheophyllinate radical has eliminated the unwanted side-effects, but until this is proved in this country I think filon should be regarded as a drug of addiction.

Pharmaceutical Department, Burnley General Hospital, Burnley, Lancashire. E. R. TALLETT.

1. Glatt, M. M. *Lancet*, 1959, ii, 348.
2. Evans, J. *ibid.* p. 152.
3. Silverman, M. *Brit. med. J.* 1959, i, 696.

RETROBULBAR NEURITIS IN ADDISONIAN PERNICIOUS ANÆMIA

SIR,—Dr. A. D. M. Smith in his letter (May 6) raises an interesting point concerning the estimation of serum vitamin B_{12} with *Lactobacillus leichmannii*.

He points out that there is a difference in the results obtained with and without the use of cyanide in the extraction process, and states that this difference is greater in non-smokers than in smokers and in patients with tobacco amblyopia. This he takes as supporting the hypothesis that in non-smokers there is a substantial amount of hydroxocobalamin in the serum, whereas in smokers most of the serum-vitamin-B_{12} is in the form of cyanocobalamin. This is an interesting observation, but its interpretation depends on the mechanism by which cyanide extracts vitamin B_{12} from serum, which is not yet fully understood.

Several workers have noted that the omission of cyanide during extraction (by heating with a buffer at pH 4–5) gives low results in the assay with *L. leichmannii*.[1–3]

I found that when 22 normal sera were estimated with *L. leichmannii*, both with and without cyanide in the extraction procedure, the values obtained in the absence of cyanide ranged from 78% to only 28% of those obtained when cyanide was present—the mean being 51%. I have also found that the low values obtained in the absence of cyanide are accounted for by loss of vitamin B_{12} in association with the protein precipitate formed during extraction.[4] If sera are extracted without cyanide, re-extraction of the protein precipitate with a cyanide-containing buffer yields substantial amounts of vitamin B_{12}. The amounts of vitamin B_{12} recoverable in this way are approximately equal to the difference in the values obtained by extraction of sera with and without cyanide (see accompanying table).

RECOVERY OF VITAMIN B_{12} BY RE-EXTRACTION OF PROTEIN PRECIPITATES OBTAINED BY EXTRACTION WITHOUT CYANIDE

Serum no.	Vitamin B_{12} ($\mu\mu$g. per ml.)			
	Serum extracted with cyanide	Serum extracted without cyanide	Loss	Recovered from protein precipitate
1	650	360	290	270
2	500	310	190	210
3	655	510	145	150
4	500	300	200	150
5	510	310	200	175

While these results show that when sera are extracted in the absence of cyanide, not all the vitamin B_{12} is estimated owing to loss in the protein precipitate, they do not explain how cyanide acts. Cyanide has two possible actions in extracting vitamin B_{12} from biological materials.[5] One is to aid the splitting of the vitamin from proteins; the other to convert hydroxocobalamin, which is relatively inactive for *L. leichmannii*, to cyanocobalamin, to which the organism responds. The results quoted do not show whether one or both of these actions are involved in the extraction of vitamin B_{12} from serum. Though in the absence of cyanide, the vitamin remains in association with the protein precipitate, which might seem to favour the " splitting " hypothesis, the possibility that some or all of this vitamin B_{12} is in the form of hydroxocobalamin has not been excluded. However, Halsted [6] found that extraction by autoclaving serum with an assay medium containing no cyanide gave values similar to those obtained by extraction with a cyanide-containing buffer. This result is hard to explain if the action of cyanide is to convert serum-hydroxocobalamin to the cyanoform. Until the mechanism of extraction is fully explained, it is therefore unsafe to assume that the difference in values obtained in the *L. leichmannii* assay with and without cyanide represents serum-hydroxocobalamin.

1. Spray, G. H. *Clin. Sci.* 1955, **14**, 661.
2. Boger, W. P., Wright, L. D., Strickland, S. C., Gvlfe, J. S., Ciminera, J. I. *Proc. Soc. exp. Biol., N.Y.* 1955, **89**, 375.
3. Killander, H. *Acta Soc. Med. upsalien.* 1957, **62**, 39.
4. Matthews, D. M. To be published.
5. Coates, M. E., Ford, J. E. *Symp. biochem. Soc.* 1955, **13**, 36.
6. Halsted, J. A. Personal communication, 1959.

It is clearly important that the action of cyanide should be elucidated as soon as possible—this, I think, is insufficiently appreciated. Further investigations may be expected to clarify whether or not appreciable amounts of hydroxocobalamin exist in the serum. It may also put an end to a confused state of affairs in which some workers use cyanide in the *L. leichmannii* assay and some do not. This leads to wide discrepancies in the values reported from different laboratories; and at present the significance of "serum-B_{12}" values obtained by extraction with buffer in the absence of cyanide is impossible to assess.

Department of Pathology,
The Royal Free Hospital,
London, W.C.1. D. M. MATTHEWS.

CAPITAL MURDER

SIR,—Victor John Terry, aged 20, atoned for his crime, on May 25, in the execution shed. Two eminent psychiatrists gave evidence at the Assize Court trial, and presented the jury with disparate opinions:

One found, from the facts presented to him, no reason, on medical grounds, to dispute the prosecution's claim of capital murder. The other, on the other hand, concluded, from the facts presented to him that, from the clinical standpoint, the prisoner was entitled to the less severe sentence because of diminished responsibility.

The time has surely arrived for the creation of a whole-time forensic medical post in psychiatry carrying consultant status. The holder of such an office could be available to investigate the mental state of prisoners awaiting trial, whenever that was called for. He or she would, in these circumstances, be in a position to arrive at a diagnosis directly, and could present this view, in evidence, as a permanent official, and not, as hitherto, as the nominee of a solicitor for either the prosecution or the defence.

The need for an appointment of this kind seems to be a near-imperative when the issue at stake happens to be, as in this instance, the life of a mere boy.

London, W.1. MURDO MACKENZIE.

COMBINED HOSPITAL AND GENERAL-PRACTICE TRAINING

SIR,—A joint selection and training committee, composed of representatives of the Newcastle Regional Hospital Board, the Durham County Executive Council, and the Durham Hospital Management Committee, has been considering how best to start a combined hospital and general-practice training scheme. A new post has been created, and it is hoped to make the first appointment this summer.

The post will be held for two years, during which the holder will spend approximately one year as a registrar in various departments of Dryburn Hospital, an acute general hospital of 304 beds in Durham City. Attachment to each department will normally last one month and will alternate with periods of at least one month as a trainee assistant to a local general practitioner. During the first eight months, one month each will be spent in the general medical wards, in the general surgical wards, in the ear, nose, and throat department, and in the pædiatric wards; also three or four periods of from one to two months in general practice as a trainee. Detailed planning of the remaining sixteen months has purposely not been attempted so that the experience of the first eight months may be profited from, and the trainee's wishes on further training considered. Accommodation will be provided at, or near, Dryburn Hospital for the trainee, whether married or single.

When he has had this experience of both hospital and general practice, he will be better able to decide on his future career, either as a general practitioner or as a hospital doctor. It is hoped that the appointment will count equally for experience, whichever career the trainee decides to follow.

Since the trainer will be a local practitioner, the trainee will often be helping to assess and treat in hospital patients whose medical and social problems are well known to him from his experience as a trainee general practitioner. Thus he will gain an overall picture of medical work within the community.

Newcastle Regional Hospital Board, Newcastle upon Tyne. R. H. M. STEWART
Senior Administrative Medical Officer.

*** Details of this appointment appear on p. 56 of the advertisements.—ED. L

SHORTAGE OF HOSPITAL STAFF

SIR,—I have read with great interest the letter of Mr. Devenish and Dr. Coghill (May 13), with much of which I entirely agree. The fact that many able and well-trained young nurses wish to give up hospital work when they complete their training speaks for itself. A review of the whole nursing service is urgently needed.

Nottingham. S. ALAN S. MALKIN.

OSTEOPOROSIS

SIR,—Having read with interest the important papers on osteoporosis by Dr. Nordin and by Dr. Harrison, Professor Fraser, and Miss Mullan (May 13), in both of which attention is focused on calcium, we should like to make a few suggestions.

It seems to us quite possible that administered calcium could be deposited in other ways. Collagen has a considerable affinity for calcium, and when bone affinity for calcium is declining, deposits in other tissues (cartilage, arterial walls, and aorta in particular [1]) and in kidney stones can become considerable. This also should lead to a positive calcium-balance and is more likely to occur in older patients than in younger ones.

There is another completely different aspect.[2] Bone apatite contains a fairly large amount of magnesium (0·7% of the total bone ash; calcium 36–38%, phosphorus 17·7–18·8%). Total bone magnesium is estimated at 20–29 g. in a 70 kg. subject. Thus, a loss of bone minerals sufficient to show on X-ray examination (30–40%) means a magnesium loss of about 8 g. A rough estimate of the amount of magnesium in the soft tissues is 8 g. But this is certainly not available for incorporation into bone. In fact the reverse is true, for the bone acts as a store from which the soft tissues and body fluids can be supplied, thus ensuring normal cell activity when magnesium intake is too low. Deficient intakes of magnesium have been reported [3–5] though these were reports of the role of magnesium deficiency in atherosclerosis, and of related problems. Animal experiments support the hypothesis that magnesium deficiency plays a role in osteoporosis. Duckworth et al.[6] found osteoporosis as well as calcium deposits in the soft tissues in rats on a magnesium-deficient diet. Smith [7] demonstrated demineralisation of bone—of the caudal vertebræ especially—in calves on a magnesium-deficient diet. Rapid improvement ensued after magnesium was given. Furthermore, large amounts of calcium, as usually given therapeutically, aggravate magnesium deficiency.[8] Magnesium requirement is also increased by high-protein diets.[9 10] A high-protein diet is advisable to promote the necessary bone-matrix formation, which in its turn is necessary to increase the affinity of the bone for calcium.

1. Fells, I. G. *Circulat. Res.* 1959, **7**, 693.
2. Dalderup, L. M. *Voeding*, 1960, **21**, 424.
3. Keeser, E. *Med. Klinik*, 1952, **47**, 542.
4. Seliger, H. *ibid.* p. 422.
5. Bersohn, I., Oelofse, P. J. *Lancet*, 1957, i, 1020.
6. Duckworth, J., Godden, W., McMartin Warnock, G. *Biochem. J.* 1940, **34**, 97.
7. Smith, R. H. *ibid.* 1959, **71**, 609.
8. Wacker, W. E. C., Vallee, B. L. *New Engl. J. Med.* 1958, **259**, 431, 475.
9. Menaker, W. *Proc. Soc. exp. Biol., N.Y.* 1954, **85**, 149.
10. Menaker, W., Kleiner, I. S. *ibid.* 1952, **81**, 377.

If bone mineralisation has to be stimulated, it should be advantageous to increase the affinity for calcium, and an ample supply of magnesium and proteins might be very helpful in this connection.

The Netherlands Institute of Nutrition, Wageningen, Amsterdam. L. M. DALDERUP C. B. M. DALDERUP.

RUPTURE OF THE POSTERIOR URETHRA

SIR,—It is significant that among Mr. Wilkinson's 12 examples of this injury (May 27), the least good results of treatment were in an 11-year-old boy. The small size of the urethra in boys may make the traction method of treatment with a Foley catheter difficult, if not impossible, to apply. Apparently the smallest Foley catheter obtainable is a no. 12 French gauge.

Faced recently with the problem of treating a complete rupture of the posterior urethra with wide separation, first in a boy of 9 and, a few months later, in a boy of 11, we resorted to an indwelling plastic catheter. Owing to the possibility of an infected impassable stricture if treatment failed we decided to keep the catheter in for 2–3 months until the patient had fully recovered from other injuries and was able to walk.

The results were satisfactory. Both boys were free from urinary infection a few days after removal of the catheter and have remained free since. Both have normal intravenous pyelograms. The younger boy has full control of micturition; the older boy, who had the more severe pelvic fracture, still has some stress incontinence. We consider it wise to pass a urethral dilator every few months, and so far, 20 months and 12 months respectively after injury, the urethra of each boy has taken a full-size instrument first time without difficulty. There is no evidence of stricture.

It appears safe to leave a plastic catheter indwelling for several weeks; and traction, though theoretically indicated to bring the ruptured ends of the urethra together, may not be essential. Moreover, retaining the catheter for a long time may prevent the dislocation of the upper end of the urethra which sometimes happens if the splinting is removed too early.

Hillingdon Hospital, Uxbridge, Middlesex. C. G. SCORER.

SKELETAL FLUOROSIS

SIR,—May I briefly reply to Mr. James (May 20)? It is difficult to understand what he means by the lower end of the category "mild fluorosis". Dr. Dean's clear definition [1] (which has been universally adopted) of this grade based on his examination of *children* is as follows:

"The white opaque areas in the enamel of the teeth involve at least half of the tooth surface. The surface of molars, bicuspids and cuspids subject to attrition show thin white layers worn off and the bluish shades of underlying normal enamel. Light brown stains are sometimes apparent generally on the superior incisors".

An appearance showing less damage would surely be placed in Dean's category of "very mild fluorosis".

The paper by Ast et al.,[2] to which Mr. James refers, has been seriously criticised by Sutton.[3] But Mr. James, while quoting their figures that 6 out of 438 children in Newburgh had "mild fluorosis", does not mention that a further 26 had "very mild" and 46 had "questionable" fluorosis. The brown stain that is "so faint as to be almost indistinct" in a child with "very mild" mottling may be quite prominent when he becomes an adult.[4] No matter what the final proportion of cases of "mild" or "very mild" fluorosis will be when properly conducted investigations have been carried out to eliminate examiner bias, examiner variability, &c., the facts remain: (1) these are the dental signs of chronic endemic fluorosis [1]; (2) fluorine is an insidious poison, harmful and cumulative in its effect [5]; and (3) the dose per person per day from water intake is scientifically uncontrollable.

Those who support fluoridation of public water might meet their scientific critics on the question of toxicity and safety if they would turn their attention to the use of *fluoride-free* compounds which recent work [6] indicates are effective in inhibiting dental caries in children *and adults*.

Institute of Pathology, The Royal Infirmary, Cardiff. R. A. HOLMAN.

THE NATURE OF VAGINAL DISCHARGE

SIR,—In his article of May 20, Dr. Boycott describes the results of his examination of 595 vaginal swabs taken from women who had complained of vaginal discharge. In a high proportion, 62%, he found that the vaginal secretion was normal. This is not surprising, and offers a very good illustration of the inadequacy of taking only vaginal swabs when investigating this complaint.

It is impossible to assess the comparative incidence of the many types of genital discharge in women, but undoubtedly cervicitis is one of the most common causes. When the discharge is cervical in origin, the vagina and the vaginal fluid may be normal. This also applies if the discharge is from the urethra, bartholinian ducts, or rectum. In these cases a cotton-wool swab inserted into the vagina may collect normal vaginal fluid only, and in fact this frequently happens. Only a properly detailed examination of the various sites of genital infection, with appropriate specimens taken from each, will lead to an accurate diagnosis.

This clinic is recognised for the treatment of venereal disease, but this does not, of course, mean that all the patients seen here are suffering from gonorrhœa or syphilis. We see many women who are complaining only of vaginal discharge and who have been referred here for investigation, or have attended of their own accord. It is only very occasionally that we find no evidence of any abnormality in a patient who complains of vaginal discharge.

Reliance on a vaginal swab alone appears to be very widespread, and has serious consequences. Firstly, very many women with a most distressing symptom are deprived of adequate treatment. Secondly, serious infections are missed—particularly gonorrhœa, which can rarely be diagnosed in a woman unless specimens taken directly from the cervical canal and urethra are examined.

The incidence of gonorrhœa has recently increased; there is little doubt that our lack of control over this condition is in some measure due to the fact that the diagnosis is so frequently missed in women.

Whitechapel Clinic, London Hospital, London, E.1. EVA GALLAGHER.

SHORTAGE OF RADIOGRAPHERS

SIR,—On behalf of the Society of Radiographers I should like to comment briefly on some points raised by Professor Johnstone in his letter (April 29).

The insistence on a pass in mathematics at ordinary level in the G.C.E. before registration as a student radiographer was a decision reached by the council of the society after full consultation between its education committee and representatives of the Faculty of Radiologists and the Hospital Physicists' Association. Experience would suggest that a student who does not possess this basic qualification is sometimes so deficient even in simple arithmetic that she does not know the meaning of "25%". Surely everyone would agree that this failing hinders the production of good radiographs or the safe handling of ionising radiations.

As a result of local experience, a number of training schools, when selecting candidates for admission, now require a pass

1. Dean, H. T. *in* Fluoridation (by F. B. Exner). New York, 1960.
2. Ast, D. B., Smith, D. J., Wachs, B., Cantwell, K. T. *J. Amer. dent. Ass.* 1956, **52**, 314.
3. Sutton, P. R. N. Fluoridation: Errors and Omissions in Experimental Trials; p. 52. Melbourne, 1959.
4. Exner, F. B. Fluoridation. New York, 1960.
5. Gross, L. *New York Times*, April 1, 1957.
6. Ritchie, D. B. *Nature, Lond.* 1961, **190**, 456.

in the G.C.E. at ordinary level in physics, in addition to the subjects stipulated by this society. Council's decision reflected the belief that, in making mathematics, rather than physics, the compulsory subject, the possibility of training would be extended to young people whose previous education had not been specifically oriented towards a scientific career.

It is usually feasible for those applicants who "have all the qualities of good radiographers" but have not passed mathematics at ordinary level in the G.C.E. to obtain this last requirement by evening courses at a technical college. To ask them to do this is not necessarily to lose them to the profession. I have known several who by a little application and persistence have successfully qualified for training.

Professor Johnstone says that in Sweden there is a "trend to do away with technical assistance", and that Great Britain will follow the Continental lead. A rather different picture is provided by the formation of the International Secretariat of Radiographers and Radiological Technicians during the ninth International Congress of Radiology, held at Munich in 1959. We know that the countries of Western Europe are at present concerned to improve their standard of training for radiographers. It was clear to the British representatives at the congress that the level which is sought by our European colleagues is that established in this country by the Society of Radiographers. It would appear to be of more than national significance that that standard should be maintained.

Society of Radiographers,
London, W.1.

D. N. CHESNEY
President.

CLEAN HANDS

SIR,—The preparation of the surgeon's hands for operating is very important both for the patient and for the surgeon. It is also of some economic interest.

The present practice of scrubbing for 5–15 minutes is perhaps based on tradition rather than any more compelling reason. Some surgeons consider that the preoperative cleansing of hands should render them sterile; and on this premise are quite prepared to touch the outside of the gown, and even gloves as they put them on. Others consider the hands to be clean but not sterile, and therefore take great care to avoid touching anything sterile with their hands, and also to keep their gloves intact during the operation. Some surgeons scrub with equal care between each operation, while others scrub once or twice during a morning's operating-list, and otherwise rely on changing their gloves. Some solution applied to the hands between glove changes sometimes supplements the security. Many solutions are used for this purpose. Presumably the object is to render the hands and forearms free from bacteria for the longest time in the simplest and most economical way which has no ill effect on the surgeon or his hands.

To improve skin preparation it was decided in 1956 to prepare the patients' skin preoperatively not with 2% iodine in spirit, as hitherto, but with a 0·05% solution of chlorhexidine ('Hibitane') in spirit.

A limited number of swabs (about 40 in all) was taken of the skin during, and at the end of, operation. No pathogenic organism was grown from any of these—the longest period of test was 2 hours. More exhaustive bacteriological tests of the skin at operation, as were done for iodine (reported by Gardner [1 2]), were not thought necessary.

This solution in well over 1000 cases has given rise to no skin reactions and no evidence has been found that the solution was in any way less suitable or reliable than iodine.

The satisfactory results obtained on skin preoperatively led us to test a similar solution for preparing hands before operation. Our group pharmacist and the makers (Imperial Chemical Pharmaceuticals) recommended a solution of 0·5% cetrimide ('Cetavlon') and 0·05% chlorhexidine in 70% spirit. We were advised that thorough exposure of socially clean hands and arms to this solution for ten seconds would ensure that they were free from organisms.

During the past year all the nursing staff and surgeons undertaking my lists and emergency procedures have prepared their hands in this way. When this method was first brought into use broth cultures were taken on twelve occasions from the hands of 14 of those working in the theatre; and 153 cultures were made. These cultures were taken from dry, "socially" clean hands before immersion in the solution; after immersion for twenty seconds in the solution; and after gloves were removed at the end of the operation. The time-interval between these last two swabs was carefully adhered to at first, but as it was always well within the five hours recommended by the manufacturers and the pattern of results was so similar, the timing was given up.

After chlorhexidine 77·8% of the cultures grew no organisms, 16·6% grew non-pathogenic micrococci, and 5·6% aerobic spore-bearing bacilli. Organisms present on the hands before immersion in the solution included *Staphylococcus aureus, Streptococcus viridans. Str. hæmolyticus, Proteus vulgaris,* and paracolon bacteria. These never appeared in the cultures taken after immersion in the solution or when gloves were removed after operation, but micrococci usually grew in cultures taken after gloves were removed. On a few occasions aerobic spore-bearers—but no pathogenic organisms—were grown. No member of the staff has shown sensitivity to the solution, or irritation from it.

The patients operated on under this regimen have been carefully watched for evidence of infection. This has been difficult to assess. Some operations were to reopen old wounds and compound fractures, others were on fresh wounds. There has been no evidence to suggest that the change has had anything but a good effect on our already low infection-rate.

It is interesting to speculate on the number of "surgical" man-hours per week in this country devoted to the ritual of scrubbing-up. If this could be replaced by a technique affording greater protection for the patient, and taking one-tenth of the time, all concerned would obviously benefit. There may be other solutions which will do the job equally well; but the solution we have tried has met in all respects the demands made on it.

I wish to thank Dr. R. L. Vollum and Dr. W. H. H. Jebb, of the department of bacteriology, for their help in the bacteriological investigations and in interpreting the results.

Accident Service,
Radcliffe Infirmary,
Oxford.

J. C. SCOTT.

1. Gardner, A. D., Seddon, H. J. *Lancet*, 1946, i, 683.
2. Gardner, A. D. *ibid.* 1948, ii, 760.

CHELATING AGENTS AND ZINC EXCRETION

SIR,—The hypocholesterolæmic action of aspirin has recently been discussed.[1–4] A similar reduction in serum-cholesterol has been reported in patients following treatment with the disodium [5] and calcium [6 7] salts of ethylenediamine tetra-acetic acid, penicillamine,[8] isoniazid,[9] British anti-Lewisite (B.A.L.),[10] hydralazine,[8] diphenylthiocarbazone,[11] and neomycin.[12]

A property common to all of these structurally dissimilar

1. Hetzel, B. S., Charnock, J. S., Lander, H. *Metabolism*, 1959, **8**, 205.
2. Reid, J. *Med. Trib.* 1960, **1**, 20.
3. Eidlitz, M. *Lancet*, 1960, ii, 1123.
4. Alexander, W. D., Macdougall, A. I., Oliver, M. F., Boyd, G. S. *ibid.* p. 1399.
5. Clarke, N. E., Sr., Clarke, N. E., Jr., Mosher, R. E. *Amer. J. med. Sci.* 1960, **239**, 732.
6. Perry, H. M., Jr., Schroeder, H. A. *J. chron. Dis.* 1955, **2**, 520
7. Perry, H. M., Jr., Perry, E. F. *J. clin. Invest.* 1959, **38**, 1452.
8. Scheinberg, I. H., Sternlieb, I. in Metal-Binding in Medicine (edited by M. J. Seven); p. 275. Philadelphia, 1960.
9. Ostrovskii, I. M., Kagan, D. Z., Iaroshevich, A. A. *Bull. Biol. Med. Exp., U.S.S.R.* 1958, **45**, 551.
10. Bobadilla, R. E. *An. Fac. Farm., Lima*, 1952, **3**, 197.
11. Lo, M. *Canad. med. Ass. J.* 1960, **82**, 1203.
12. Samuel, P. *Proc. Soc. exp. Biol., N.Y.* 1959, **102**, 194.

agents is their ability to bind metal ions.[13] Aspirin (sodium acetylsalicylate) is absorbed from the gastrointestinal tract unchanged, but in the blood is hydrolysed to salicylic acid,[14] an effective chelating agent.[15] The specific mode of action of these agents, which results in the reduction of serum-cholesterol, is unknown. Out of the above compounds, ethylenediamine tetra-acetate [16] and penicillamine [17] are not metabolised, but probably function exclusively as chelating agents. Of interest in this respect is the marked zincuria after giving intravenous calcium ethylenediamine tetra-acetate [7] and B.A.L.,[18] and the concomitant reduction in serum-cholesterol.[7]

Daily urinary zinc [19] excretion was measured in an individual clinically free of disease, before, during, and after aspirin medication. The findings are summarised below:

Day	*Aspirin (gr.)*	*Volume ml. per day*	*Zinc µg./day*	*Zinc µg./litre*
1	0	1290	823	638
2	0	1140	455	399
3	60	1070	1953	1824
4	60	1250	2595	2076
5	60	1025	2411	2351
6	60	1170	2173	1857
		4-day interval		
1	0	975	691	707
2	0	1035	390	377
3	60	1260	2605	2067
4	60	1150	2727	2370
5	60	1320	2209	1673
6	60	1210	2620	2051
7	0	1010	1053	1048
8	0	1125	1035	920

The data indicate that aspirin medication (as salicylic acid) is associated with a marked zincuria. Before medication with aspirin the subject's serum-cholesterol was normal, and remained essentially unchanged throughout the medication period. Preliminary laboratory evidence indicates that 10^{-4} *M* zinc solution inhibits lipoprotein lipase,[20] an enzyme required for normal fat transport. It is not clear whether zinc interferes with the apoenzyme, or the coenzyme, pyridoxal phosphate,[21] but the latter appears most likely.

Albany, New York. O. W. WENDEL.

ADVANTAGE OF LEFT LATERAL POSITION FOR PALPATING THE GALLBLADDER

SIR,—A distended gallbladder is more easily palpable with the patient in the left lateral position; and one not palpable in other positions may then be felt. This is illustrated by the following case.

A man of 62 with obstructive jaundice was suspected of having carcinoma of the pancreas, as a barium meal finding of a widened concavity of the duodenum suggested enlargement of the head of pancreas. In the supine and sitting position, no tumour could be felt in the abdomen, nor any enlargement of the liver or gallbladder; but the patient reported that recently he had felt abdominal swelling but only when he lay on his left side. When he assumed this position a swelling was clearly palpable behind the right rectus muscle. In the supine or sitting position this swelling disappeared. After about 10 days the swelling became larger and just palpable in the supine and sitting positions; but it was still better felt in the left lateral position. The lump was presumed to be a liver metastasis from a pancreatic tumour.

But at laparotomy I found that the swelling was a simple distended gallbladder (pyocele) with a calculus in Hartmann's pouch. The gallbladder was removed and the patient recovered.

I tried to find out whether the enlarged liver is palpable earlier in the left lateral position than in the supine or sitting position; and this is indeed the case.

A probable explanation is that, since the right lobe of the liver is six times bigger than the left, when the patient lies on his left side the liver is likely to be displaced to this side by gravity; hence in this position the chest can expand more freely on the right side so the diaphragm is likely to push the liver downwards much more in this position than when the patient is supine or sitting.

Department of Surgery,
M.S. University,
Baroda, India. M. A. PATEL.

SERUM-LEUCINE-AMINOPEPTIDASE IN SNAKE-BITE

SIR,—In the past few years the determination of leucine aminopeptidase (L.A.P.) in serum and urine has become an accepted procedure in the diagnosis of pancreatic carcinoma and various causes of jaundice.

We have performed this test in 130 different cases.[1] We compared our two methods,[2 3] which are based on the principles originally described by Goldbarg and Rutenburg,[4] and they gave identical results.

We found the normal values of serum-L.A.P. to range from 55 to 220 G.R. units. Normal values of serum-L.A.P. were obtained in nearly all conditions not connected with the pancreas, liver, or biliary tract, and in nearly all cases of non-obstructive liver disease. Increased values of serum-L.A.P. were found in all cases of benign obstructive jaundice, and of carcinoma of the pancreas.

To our surprise, significantly high values of serum-L.A.P. were also found in 10 out of 12 cases of snake-bite. The estimations were performed in the first 24-48 hours after the bite, and none of the patients was jaundiced. The patients were treated with antivenene, antihistaminics, and steroids. There were no deaths.

The increase in serum-L.A.P. levels was found to parallel the severity of the symptoms.

Case no.	*Serum-L.A.P. (G.R. units)*	*General condition*	*Swelling of the extremity*
1	95	good	++
2	178	good	+
3	235	good	−
4	284	good	+
5	288	good	++
6	296	good	++
7	324	good	+++
8	335	good	+++
9	360	good	+++
10	370	fair	++
11	410	bad (collapse)	++++
12	417	bad (collapse, diarrhœa)	++++

− No swelling; + local swelling; ++ swelling up to the elbow or knee; +++ swelling extending above the elbow or knee; ++++ severe swelling up to the neck.

The small number of cases does not allow statistically significant conclusions to be drawn.

It is not clear whether the rise in the serum-L.A.P. is due to liver damage or to interference by the venom with enzyme systems.

Chemical Laboratory,
Asaf Harofe Government Hospital,
Zerifin, Israel. J. FISCHL.

Medical Department B,
Asaf Harofe Government Hospital,
Zerifin, Israel. W. PRUZANSKI.

ELIZABETH GARRETT ANDERSON

Miss J. G. MANTON, M.A. writes:

"I have been commissioned to prepare a detailed biography of Elizabeth Garrett Anderson, M.D., to be published at the centenary of her British qualification in 1965, and I am anxious to trace any documents relating to her career. If any of your readers have autograph letters, or other papers, which they would be kind enough to lend, these would be copied, promptly returned, and of course fully acknowledged at publication. My address is 44, Westgate, Chichester, Sussex."

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21. Unpublished data.

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2. Frankel, S. *Lab. Dig.* 1959, **22**, no. 10, 5.
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Medicine and the Law

Advertisement and Information

A CONSULTANT ear, nose, and throat surgeon, who had practised cosmetic surgery for some years, wrote and caused to be published a book, and sanctioned and acquiesced in the adapted and embellished serialisation of the book in a women's magazine with a mass circulation, receiving and approving galley proofs of the articles, for which he was paid.

The book, autobiographical in form, described how the author came to be concerned with cosmetic surgery, explained its nature, and gave accounts of many successful operations performed by him. It proclaimed that there need be no prejudice against cosmetic surgery, that it might be resorted to without fear, and that the author was one who by his training, skill, and experience had brought relief and happiness to his patients. The wrapper on the book carried a photograph, and set out the scope of the contents.

The surgeon was charged before the Disciplinary Committee of the General Medical Council with advertising for the purpose of obtaining patients or promoting his own professional advantage, and was found guilty of infamous conduct in a professional respect in three ways: by writing and causing the book to be published; by sanctioning or acquiescing in an introductory article about himself introducing the serialisation in the magazine; and by procuring or sanctioning the publication of the articles, all of which were alleged to include matter directing attention to his professional skill, knowledge, services, and qualifications. The committee directed that his name should be erased from the Register.[1] The surgeon appealed to the Judicial Committee of the Privy Council; and on the hearing of the appeal their Lordships allowed his request that certain other publications, including many issued under the sponsorship of the British Medical Association, and press articles and interviews as recorded in the Press, should be considered by their Lordships.

Lord MORRIS OF BORTH-Y-GEST, giving their Lordships' advice to Her Majesty, said that the particulars of the charges did not refer solely to the fact that the book and the articles were published but that they "included matter directing attention to your professional skill, knowledge, services and qualifications". It had therefore been necessary for the Council and for their Lordships to consider the nature of the written material, the mode of publication, and all the circumstances relating to the purposes and reasons which inspired the publication.

It must be recognised that professional medical men might be amply justified in publishing books and articles and doing so in their own names. By their writings they might be making invaluable contributions to medical science and learning, disseminating useful knowledge, helping their fellow practitioners, and advantaging a wider public. It must, however, be recognised that by their writing they might inevitably and indeed justifiably attract notice. That might redound to their professional and pecuniary advantage. But within the profession the line between the kind of publication which was unobjectionable and that which was objectionable should present no difficulties for any reasonable practitioner. The accepted ethical standards might not be formulated in any written code, but they were quite clearly within the comprehension of qualified and experienced members of the profession. The Disciplinary Committee's practice was to issue a "Warning Notice" for the guidance of registered and provisionally registered practitioners against advertising, either directly or indirectly, for the purpose of obtaining patients or of promoting personal professional advantage. The appellant had received a copy of such notice in May, 1954.

Examples might be given. On one side of the line there might be a book or article expounding a particular subject, such as a textbook for medical students, or written impersonally to give information to the general public. No exception could be taken to such publication. On the other side of the line there might be a book or an article, an essential theme of which was the praise and commendation of the skill and abilities of the writer himself, with an express or implied suggestion that his successes in dealing with cases showed that potential patients would do well to have recourse to him. That would be "advertising". It might be entirely proper, in the case of a book or article written impersonally as an exposition of a medical subject or to convey valuable general advice, not only that the name of the writer should appear but that, possibly on a wrapper, there should be some factual mention of his position and attainments. But that would be in contrast to a book or article written in the hope and with the purpose of attracting patients; for that would be self-advertisement, to which exception could properly be taken.

Before the committee the appellant had plainly said that he had had more than one purpose in writing. Their Lordships recognised that while in some cases a particular purpose might be exclusive there might be cases in which a particular purpose might be merely incidental. It seemed to them that in finding that the facts alleged against the appellant were proved the committee must be taken to have held that in publishing his book and sanctioning the publication of the articles he had to a substantial extent the purpose of obtaining patients or promoting his own professional advantage.

On the additional material considered by their Lordships at the appellant's request, they had been referred to the biographical and commendatory notes with photographs appearing on the backs of certain books written for laymen on medical subjects by medical men for a well-known popular series of books; and the appellant had referred to some of these as denoting what he submitted he was entitled to regard as legitimate conduct in medical men of good repute and competence. Their Lordships were not called on to express any opinion in regard to any other book or article, or in regard to any newspaper report of interviews; but they had noted certain manifest contrasts between such of the publications containing medical advice as had been seen by them and the book written by the appellant, together with the articles in the women's magazine.

The appellant had testified in his evidence that one of his purposes in writing his book was to dispel and terminate a certain veil of secrecy which he said had shrouded cosmetic surgery, and that another purpose was to combat the "subversive propaganda" that eight or nine members of a syndicate were the only accredited people who could operate. Their Lordships considered that the Disciplinary Committee were entitled to decide that in carrying out those purposes the appellant had had the essential purpose of presenting himself and his subject to the public and proclaiming himself as a cosmetic surgeon whose services the public might be well advised to seek. That would furnish ample warrant for the conclusion that he had had to a substantial extent the purpose of obtaining patients or of promoting his own professional advantage. But, quite

1. See *Lancet*, 1960, i, 1243.

apart from that, the committee were entitled to have regard to the content and form of the written material and the selected media for its publication, in forming their conclusions as to what were the purposes which animated the writer; and they were entitled also to consider whether a desire to give information about, and direct attention to, a particular subject could have been achieved without directing attention to the personal and unique performance and abilities of the writer. Having been fully referred to the evidence and the articles and having considered the book, their Lordships saw no error in the decision of the Disciplinary Committee. The appeal should be dismissed.

Gardiner *v.* General Medical Council—*Judicial Committee of the Privy Council:* Lord Tucker, Lord Denning, and Lord Morris of Borth-y-Gest: May 31, 1961. Counsel and Solicitors: The appellant in person (Henry Solomon & Co.); Peter Boydell and Hugh Carlisle (Waterhouse & Co.).

M. M. HILL
Barrister-at-Law.

Parliament

Learned Societies' Rates

DURING the debate on the second reading of the Rating and Valuation Bill in the House of Lords on May 31, several peers expressed their concern about the heavy burden which the Bill would throw on many scientific societies. In his reply Lord HAILSHAM, Lord President of the Council and Minister of Science, was able to give some reassurance. He had received a deputation from the learned societies, and there was prospect of fairly general agreement on how the problem should be tackled. He felt himself that the answer might not be rate-relief but some form of grants. He would consider using the Royal Societies and the British Academy as vehicles for this kind of negotiation, and if they were prepared to act the Government would be glad to hear from them, as and when the situation developed.

QUESTION TIME

Intake of Medical Students

Mr. ROBINSON asked the Minister whether he was reviewing, in the light of the current and future needs of the National Health Service, the conclusions of the Willink Committee on the intake of medical students, and if he would make a statement on future policy in this respect.—Mr. POWELL replied: The Secretary of State for Scotland and I are reviewing the data and calculations which underlie the estimates in the Willink Committee's report. The student intake is larger now than when the committee reported. Mr. ROBINSON: I am glad to know that the Minister is reviewing this, but would he now appreciate that this was one of the most disastrous reports upon the health service ever acted upon by his department, and will he now agree with the view of eminent people that there is a shortage of doctors in the National Health Service?

Shortage of Doctors

Mr. BOYDEN asked the Minister of Health in what areas, and in what specialties, there was a shortage of doctors in Great Britain in 1960.—Mr. POWELL replied: Vacancies in the grades of registrar and below were slightly under 9% of posts, varying between 6% and 17% in different regions, but some vacancies were filled by locums. In senior grades there were few vacancies apart from those arising in the ordinary course. Mr. BOYDEN: What long-term steps are being taken to remedy this state of affairs? In view of the founding of more universities, is the Minister having discussions with the University Grants Committee with a view to founding new medical schools in these universities?—Mr. POWELL: Starting new schools is not a matter for me but some estimation of the requirements of the health service is.

Mr. KENNETH ROBINSON: Regarding the shortage of consultant posts, would not the Minister agree that the statement of the number of vacancies is not a fair assessment of the position since large numbers of regional boards want additional posts established which his own department does not permit them to establish?—Mr. POWELL: Vacancies are the only statistical figures which I have available. But the number of posts in 1960 for which approval was withheld because there were no applicants available to fill them is comparatively few.

Prescription Charges

Mr. R. W. MARSH asked the Minister of Health how many executive councils had protested to him about the increase in prescription charges.—Mr. POWELL replied: 48.

Mr. L. A. PAVITT asked the Minister if he would now reconsider the amount charged for items of prescription in the light of the 20% decrease shown by the fall from 22,200,000 items in February, 1961, to 17,500,000 items in March, 1961.—Mr. POWELL replied: No, Sir.

Mr. KENNETH ROBINSON: The Minister estimated a 2% fall in prescriptions. He has here a 20% drop. Does he not appreciate that this compares not only with the 2% that he estimated, but with the actual increase between February and March of last year? Is not this abundant evidence that people are not getting the prescriptions they need?—Mr. POWELL: One cannot take individual months without regard to the circumstances, and certainly nothing less than the experience round the whole year can disclose any trends which are capable of being interpreted in that way. Sir HUGH LINSTEAD: In view of the differing evidence and opinions which have been expressed, and the fact that we have had some months' experience of the new charge, might it not be wise for the Minister to initiate some inquiry to try to find out what the situation is today? Mr. POWELL: I still think that it is too early for anything of that sort, but I am sure that the professions and the bodies which administer the Service will bring to my attention any evidence which comes their way.

Effects of Alcohol

Mr. GRESHAM COOKE asked the Minister if he would introduce legislation to prevent the sale of tablets purporting to modify the effects of alcohol.—Miss EDITH PITT replied: No, Sir.

Mr. GRESHAM COOKE: Is my hon. Friend aware that pills called 'Soberettes' are on sale in pubs and sweet shops, which are banned by the Pharmaceutical Society from being sold in chemists' shops, which might give the impression that drunken motorists can cure themselves from alcoholism by taking these pills? Is it not wrong that this sort of pill, which gives no evidence of any content, should be on sale giving a false assurance to people that they might be cured? Miss PITT: I am aware that such tablets are on sale. It is not quite correct to say that the Pharmaceutical Society has banned them. It has issued a notice advising chemists ". . . in view of the possibility of misuse and the consequent danger to the public . . ." they should not stock or sell these preparations, but the evidence available does not suggest that they are medically harmful.

Hammersmith Hospital Appointment

Mrs. JOYCE BUTLER asked the Minister of Health if he had now reached a decision with regard to an inquiry into the appointment of a new secretary to the board of governors of the Hammersmith Postgraduate Teaching Hospital.—Mr. ENOCH POWELL replied: Having obtained a full statement from the board of governors on the circumstances surrounding this appointment, I have come to the conclusion that they disclose no reason for an inquiry. I have so informed the Institute of Hospital Administrators, which had asked me to set up an inquiry, and have sent it a copy of the statement.

Riding for Crippled Children

Mr. R. S. RUSSELL asked the Minister if he was aware that some crippled children living in the London area were being helped to overcome some of their disabilities by being taught riding; and what steps he was taking to assist such training so that it could be developed on a larger scale.—Miss EDITH PITT replied: The Minister understands that at least one voluntary organisation and, with voluntary help, two hospitals have made

limited arrangements. He is advised that there is insufficient evidence to justify any general recommendation of riding as a form of remedial exercise instead of other methods.

Doctors and Unemployment Benefit

On June 3, 1961, there were 30 doctors on the professional and executive register in receipt of unemployment benefit.

Obituary

GEORGE MURRAY GRANT
M.B. St. And.

Dr. G. M. Grant, who was killed in a car accident at Beattock, Lanarkshire, on May 8, had been consultant radiologist to Dundee Royal Infirmary for 36 years. He was 68 years of age.

He was born at Nelson, Lancashire. He moved to Dundee as a boy and qualified M.B. at St. Andrews University in 1915. During the 1914–18 war he served with the R.A.M.C. On his return to civilian life he specialised in radiology, and he was appointed consultant radiologist to Dundee Royal Infirmary in 1924. He was also visiting radiologist to Forfar Infirmary and lecturer in dental radiology to the Dental Hospital, Dundee. When he retired last year he was appointed consultant emeritus to the Infirmary. In his retirement he and his wife planned to visit their two sons in Canada, and it was on the first stage of their journey that the accident happened.

W. C. S. writes:

"Dr. Grant's opinion was always carefully given and respected. His work was meticulous. Apparatus which did not function properly annoyed his engineering instincts and attention to detail was part of his nature. He was a former president of the Dundee Medical Club, and Rotarians will long remember his happy ability to propose a vote of thanks at a moment's notice. His colleagues will remember him with affection and respect."

Dr. Grant is survived by his widow, a daughter, and two sons, one of whom is a surgeon in Winnipeg.

HENRY GEORGE PINKER
F.R.C.S.

Mr. H. G. Pinker, consulting surgeon to the Prince of Wales Hospital, Plymouth, died at his home at Countess Wear, Exeter, on June 1, at the age of 84.

He was the son of the sculptor H. P. Hope-Pinker and he was educated at St. Paul's School and St. Bartholomew's Hospital. After qualifying in 1900 he became house-surgeon to H. T. Butlin and C. B. Lockwood. Lockwood was Pinker's hero and he copied many of Lockwood's mannerisms. In 1911 he went into practice in Plymouth, and during the 1914–18 war he served with the R.A.M.C. and became a member of the surgical staff of the South Devon and East Cornwall Hospital, Plymouth. In 1932 he took the F.R.C.S. and some years afterwards he joined, as surgical partner, the firm of Dr. Crump and Dr. Thomas at Welshpool. He continued to work there until 1951 when he retired to live at Countess Wear.

A colleague writes:

"Pinker was a most generous, kind, and hospitable man, though he could be outspoken and uncompromising. He also possessed unflagging perseverance and courage. Not many men have achieved their fellowship in surgery at the age of 55 and for Pinker it was a triumph and the attainment of a long-cherished ambition. All who knew him will remember with affection his lovable and colourful personality."

In 1912 Mr. Pinker married May, daughter of the Rev. Walrond Clarke. She survives him with their only son.

Sir HUGH GRIFFITHS

G. R. F. writes:

"I came to know Sir Hugh Griffiths well during the last seven years of his appointment at the Albert Dock Hospital before his retirement in 1956. No young consultant could have had a kinder or more loyal senior colleague. He was a man of shrewd and rapid judgment and once given the facts he could come to a decision with charm and ready wit. He could not abide the second-rate and he would not hesitate to take appropriate action if he felt that the patient's welfare was in jeopardy. His knowledge of injury in relation to function was encyclopædic, and the Albert Dock Hospital was the consummation of his pioneering efforts. We who were associated with him are proud to continue the great traditions which he established there."

Appointments

AIDNEY, CONSTANCE, M.B. Birm.: part-time M.O., maternity and child-welfare clinics, Birmingham.
COGAN, J. F., M.B. Manc., F.R.C.S., D.O.: part-time consultant ophthalmologist, Chester Royal Infirmary.
CONNOLLY, JOHN, M.B. N.U.I., D.P.H.: assistant M.O. and assistant school M.O., Rotherham.
DYER, J. V., M.B. Lond., D.P.H.: senior assistant M.O.H. (mental-health services), Northamptonshire.
FEA, P. M., M.B. Edin., D.P.H.: assistant county and school M.O., West Sussex.
FREEMAN, MARIE J., M.B. Lond.: deputy M.O.H., Buckingham.
GARRETTS, MAURICE, M.B. Lond., M.R.C.P.: consultant dermatologist, Manchester Regional Hospital Board and the Board of Governors of the United Manchester Hospitals.
JONES, J. T., M.B. Wales, D.P.H.: deputy M.O.H. and deputy principal school M.O., Lincoln.
KERR, E. S., M.B. Cantab., D.OBST.: assistant county and school M.O., West Sussex.
MEYER, NINA, B.M. Oxon., D.P.M.: consultant psychiatrist, Tottenham child-guidance and infant-welfare clinic.
POMRYN, B. A., M.B. Lond., D.P.M.: consultant psychiatrist/deputy medical superintendent, Littlemore Hospital and Ashhurst Clinic, Oxford.
VEITCH, M. A., M.B. W'srand: part-time assistant chest physician, Epping and Harlow chest clinics.

East Anglian Regional Hospital Board:

MARKEY, G. B., M.B. Adelaide, F.R.C.S.E.: surgical registrar, Norfolk and Norwich Hospital.
STOVIN, P. G. I., M.B. Cantab., M.R.C.P.: consultant pathologist, Papworth Hospital.
SUPPAL, S. K., M.B. Calcutta, M.R.C.O.G.: registrar in obstetrics and gynæcology, West Norfolk and King's Lynn General Hospital.

Leeds Regional Hospital Board:

EDWARDS, A. T., M.B. Aberd.: consultant in pathology, Halifax.
NEWCOMBE, C. P., M.D. Lond., M.R.C.P.: consultant in general medicine, York.
TOVEY, L. A. D., M.D. Brist.: consultant in pathology, Bradford.
WILLIAMS, R. G., M.B. Lond., F.R.C.S., D.L.O.: consultant in otolaryngology, Hull, East Riding, and Goole.

Newcastle Regional Hospital Board:

COWLEY, ROWLAND, M.B. Durh., F.R.C.S.E., D.O.: consultant ophthalmologist, South and North Tees-side hospital groups.
FIDDLER, G. S., M.B. Edin., D.P.M.: assistant psychiatrist (S.H.M.O.), Cherry Knowle Hospital, Ryhope, Sunderland.
SACKWOOD, MARK, M.B. Lond., D.OBST., D.P.H.: assistant senior administrative M.O., on headquarters staff.
STEVENSON, C. J., M.D. Lond., M.R.C.P.: consultant dermatologist, Newcastle upon Tyne hospital group and United Newcastle upon Tyne Hospitals.

Western Regional Hospital Board, Scotland:

CAMPBELL, DONALD, M.B. Glasg., F.F.A. R.C.S., D.A.: consultant anæsthetist, Glasgow Royal Infirmary.
FINN, O. A., M.D. Glasg.: consultant dermatologist, Stirling/Falkirk/Alloa area.
SOUTTER, FELICITY E., M.B. Edin., F.R.C.S.E.: consultant orthopædic surgeon at Stonehouse Hospital (but attached to the orthopædic department at Law Hospital, Carluke).

Colonial Appointments:

CONWAY, C. G., M.B. Dubl.: M.O., Bahamas.
DONEGAN, P. J., M.B. N.U.I., D.A.: M.O., Bahamas.
HOLGATE, J. E., M.B. Lond., F.R.C.S.: surgeon specialist, Grenada.
NICHOLSON, C. C., M.B. Edin., D.P.H.: director of medical services, British Guiana.
REES, W. H., M.R.C.S., D.T.M. & H.: S.M.O., New Hebrides.
SOMERVILLE, G. W., M.B.: pre-registration house-officer, Bahamas.

Births, Marriages, Deaths

DEATH

MANSON.—On June 1, suddenly, at 30, Hoodcote Gardens, London, N.21, Malcolm Manson, M.C., G.M., M.A., M.D.

Notes and News

CONTROL OF CONCEPTION

AT the annual meeting of the Family Planning Association on June 2–3, Dr. GERALD SWYER presented a report from the Oliver Bird Trust, whose object is to investigate simpler forms of contraception. Last year the Council for the Investigation of Fertility Control (C.I.F.C.), set up by the Trust, was asked to sponsor trials and to make recommendations about the future use of oral contraceptives, as tested in the United States and Puerto Rico by Dr. Gregory Pincus, Dr. John Roch, and Dr. Edward Tyler. The first trial of a product, by G. D. Searle, was started last June in Birmingham and is still going on; it was followed in the autumn by another at Slough. 114 women are taking part, and much useful information has emerged about the lowest effective dose of norethynodrel and the proportion of women who develop side-effects. "There is no doubt that, when given in the right dose, this is a very effective method of birth control; and the side-effects, although occasionally troublesome at the beginning, appear to be quite harmless. The pill does not adversely affect subsequent fertility. Few patients have withdrawn from the trials and many have mentioned the confidence and relaxation this method of birth control brings to their marital relationship." Meanwhile other steroids which also rely on inhibiting ovulation have had preliminary tests. They are now to be tried further at a central oral contraceptive clinic at 64, Sloane Street, S.W.1, to which volunteer patients may be referred by general practitioners and Family Planning clinics in Greater London. "We need 100 patients under 40 years of age who have already proved their fertility and are willing to attend the clinic for periodic examinations. The ideal simple contraceptive has not yet been found, and, whilst much research work continues with this object in mind, patients who volunteer to take part in C.I.F.C. trials are helping immensely towards the satisfactory solution of this problem."

The winner of the Oliver Bird prize for 1960, Dr. HAROLD JACKSON of the department of experimental chemotherapy at the Christie Hospital and Holt Radium Institute, spoke of the further progress of work which we have already mentioned.[1] Substances have been found which exert selective effects on male fertility in the rat, acting at different stages of sperm development. More recent substances have a selective action on later stages, without apparently interfering with sperm production or libido. In the rat they are active by mouth in repeated small doses, are 100% effective, and are rapid in action; and the antifertility effects are fully reversible. Their chemical structure is simple and they are inexpensive. So far there has been no evidence of serious toxic effects, but the possibility of later toxic effects needs to be explored with great care.

In his presidential address, Sir RUSSELL BRAIN spoke of the opportunities before the Family Planning Association. Now that it has become "respectable" and has the support of a vast and influential body of public opinion, there is a constant demand for more clinics. Last year 25 new ones were opened; and the Association must be prepared to take further strain. The second opportunity will emerge from the rapidly developing and growing knowledge of non-mechanical methods of contraception: "when, wherever you live in the world, you can have children only when you wish, that will be a revolution with more far-reaching effects on the pattern of human culture than the discovery of atomic energy". Thirdly, Sir Russell spoke of the opportunity to help patients over the psychosexual problems presented during normal birth-control sessions—a matter which will have to be taken very seriously. "Some of you may feel that this is all part of a service already provided by the State under the National Health Service Act, and theoretically you would be right. But I doubt, apart from a number of well-known exceptions, whether it is possible to produce elsewhere than in one of our clinics, quite the atmosphere which encourages patients with psychosexual difficulties to unburden themselves of these problems."

Mrs. PETER MEDAWAR said that the quarter of a million patients helped last year in the 340 clinics run by the Association (four-fifths of them are run on local-authority premises) regard their clinics as a natural part of the available social services. But what of the thousands who live far from the nearest clinic or are "afraid to go there"? These people can be helped only by more clinics and by more information.

Prof. FRANÇOIS LAFITTE, who is chairman of a working party which is studying the Association's future constitution, organisation, and services, said that the F.P.A. grew up as a movement of women for women; and even today it would collapse without the voluntary work of 4300 women serving on its committees and in its clinics. This inherited feminine character may handicap the Association in the era ahead, unless it can strengthen its partnership with the medical profession, grow into a joint movement of men and women serving married couples, and enlarge its use of paid administrators. The F.P.A.'s view of the essentially medical nature of advice and help with birth control, subfertility, and psychosexual problems is gaining wider medical support—as shown by the fact that so many F.P.A. clinics are in local-authority or hospital premises. But the medical profession is still lagging behind public needs and public opinion: the doctors have never held an official "Lambeth Conference" to match the Church's solemn blessing of birth control. The Association must not rest till the whole medical profession is awakened to its responsibilities, every doctor and nurse is equipped with basic training in family planning, and every branch of the medical services provides advice as a matter of course.

1. See *Lancet*, 1960, i, 156.

University of Cambridge

On May 27 the degree of M.CHIR. was conferred on A. G. Norman and of M.B. on E. R. Williams and B. E. H. Maden.

A course on the treatment of cancer, with special reference to radiotherapy and chemotherapy, arranged by Prof. J. S. Mitchell, will be held from Sept. 20 to 23. Registration forms may be had from the secretary, Medical School, Tennis Court Road, Cambridge. The course fee will be £5 5s.

University of London

Mr. H. D. Ritchie, assistant director of the surgical unit at the London Hospital, has been appointed to the university readership in surgery at the London Hospital Medical College.

The degree of M.D. has been conferred on Julius Lee.

University of Edinburgh

Dr. P. G. Gaskell has been appointed lecturer in the general-practice teaching unit, and Dr. J. R. Smythies senior lecturer in the department of psychological medicine.

University of Glasgow

Dr. J. A. Milne has been appointed reader in dermatology at the Western Infirmary.

Queen's University of Belfast

Lady Dixon has given £10,000 for medical research.

Royal College of Surgeons in Ireland

A Faculty of Radiology has been instituted in the college. The following have been appointed to its first board:

Dean, Mr. D. J. Riordan; vice-dean, Dr. S. J. Boland; hon. secretary, Dr. Finbarr Cross; other members, Dr. W. J. McHugh, Dr. D. C. Porter, Dr. T. O'Keefe, Dr. R. A. Reynolds, Dr. J. A. Geraghty, Dr. T. D. O'Farrell, Dr. D. O'Sullivan, Dr. T. P. Eustace, Dr. H. J. Henderson, Dr. E. G. Redman, Dr. J. C. Courtney, Dr. M. J. Brady, Dr. Oliver Chance, and Dr. J. J. Magner.

The faculty will institute courses of postgraduate teaching and will hold examinations for the fellowship of the faculty and for the diploma in radiology. In the first instance the council of the college will appoint a limited number of senior radiologists to be fellows of the faculty without examination. Those who wish their claims to be considered should write to the registrar of the college, St. Stephen's Green, Dublin, before Jan. 1.

St. Bartholomew's Hospital, London

On May 30 the Queen visited the hospital and declared open the Queen Elizabeth II wing of special department wards, Gloucester House, and the new radiotherapy department.

Medical Research Council

Sir Christopher Andrewes is retiring, and Dr. Alick Isaacs is to succeed him as head of the division of bacteriology and virus research at the National Institute for Medical Research. Dr. H. G. Pereira will be in charge of the World Health Organisation World Influenza Centre, which is also at the Institute.

West London Hospital Medical School

Prof. A. J. Harding Rains will give an Alex Simpson Smith lecture on Thursday, June 22, at 5 P.M., at this hospital, Hammersmith Road, W.6. His subject will be researches concerning the formation of gallstones.

Society of Apothecaries

Faculty of the History of Medicine and Pharmacy.—The first Maccabæan prize and medal, an annual prize endowed by the Maccabæans, and awarded by the faculty, has been awarded to Dr. J. K. Wales.

British Tuberculosis Association

The annual conference of this Association and the Tuberculosis Society of Scotland is to be held from June 29 to July 1, in Edinburgh. Further particulars may be had from the administrative secretary of the Association, 59, Portland Place, London, W.1.

National Institute of Industrial Psychology

Dr. R. B. Buzzard, a member of the scientific staff of the Medical Research Council, has been appointed research director of the institute.

Association of Psychiatric Social Workers

The general meeting of this Association is to be held on Saturday, June 24, at 3 P.M., at the Cowdray Hall, Henrietta Place, London, W.1, when the Earl of Feversham will give a presidential address. His subject will be the changing pattern of mental health services.

Royal Medical Foundation of Epsom College

The annual general meeting of the governors of Epsom College is to be held on Wednesday, July 19, at 3.30 P.M., at the Medical Defence Union, Tavistock House South, Tavistock Square, London, W.C.1.

Medical Association for the Prevention of War

A conference on the pathogenesis of war is to be held by this Association from July 14 to 16 at Newnham College, Cambridge. Further particulars may be had from the secretary, Dr. Dorothy Arning, 127, King Henry's Road, London, N.W.3.

Nutrition Society

On Saturday, July 15, at 11 A.M., at the Laboratory of Physiology, Oxford, this society is to hold a symposium on nutrition and metabolic defects. The speakers will be Dr. H. M. Sinclair, Dr. Philip Evans, Dr. L. I. Woolf, Prof. J. N. Cumings, Dr. Paul Fourman, and Prof. A. C. Frazer. Further particulars may be had from the hon. programmes secretary of the society, Miss D. F. Hollingsworth, c/o Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London, S.W.1.

Work of the Academy of Religion and Mental Health in the U.S.A. and Relevant British Experience

The National Association for Mental Health, in collaboration with the Churches' Council of Healing and the Central Churches Group of the National Council of Social Service, is to hold a meeting on this subject on Monday, June 26, at 3 P.M., at 1, Wimpole Street, London, W.1. The speaker will be the Rev. George C. Anderson, who is director of the Academy of Religion and Mental Health in New York. Further particulars may be had from the conference secretary of the National Association, 39, Queen Anne Street, London, W.1.

Cardiological Congress in Yugoslavia

The third Yugoslav Congress of Cardiology, held from April 22 to 25 in Opatija, was attended by about four hundred physicians from Yugoslavia and delegates from France, Belgium, Greece, Poland, the United States of America, and Great Britain. Special sessions were devoted to social cardiology, rheumatic heart-disease, and cardiac surgery.

Eleanor Roosevelt International Cancer Fellowships

The International Union Against Cancer, through funds made available by the Eleanor Roosevelt Cancer Foundation, will award annually fellowships for research on cancer.

These will be postgraduate awards for full-time members of the staff of universities, teaching hospitals, research laboratories, or other institutions, who wish to study in another country. The duration of the fellowships ordinarily will be one year, and the stipend will be based on the current salary of the applicant and on comparable salaries in the place where he expects to study. An allowance will be made for dependants and for travel. Application forms may be had from the International Union Against Cancer, P.O. Box 400, Geneva 2, Switzerland.

Air Vice-Marshal T. C. MacDonald has been appointed honorary physician to the Queen in succession to Air Commodore G. W. McAleer who is retiring.

A symposium on chest diseases in children is to be held on Wednesday, July 26, at 11.30 A.M., at Whittington Hospital, Archway Wing, London, N.19, when the speakers will be Dr. Edwin L. Kendig, Jr. (Richmond, Virginia), Dr. Warren S. Chernick (Philadelphia), and Dr. L. B. Strang.

Dr. William Buchanan has been awarded an international postdoctorate research fellowship by the National Institutes of Health, U.S. Public Health Service.

The annual general meeting of the Multiple Sclerosis Society is to be held on Wednesday, June 14, at 6 P.M., at Livingstone Hall, 11, Carteret Street, Broadway, London, S.W.1., when the speaker will be Dr. L. A. Liversedge.

The *Lancet* Cup (scratch medal) was won at the summer meeting of the Medical Golfing Society, held at St. George's Hill, by Dr. Donald Holmes (h'cap 1) with a score of 76.

Diary of the Week

JUNE 11 TO 17

Monday, 12th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Stress and Psychosomatic Illness.

INSTITUTE OF DERMATOLOGY
5 P.M. (32, Welbeck Street, W.1) Mr. R. E. Ellis: Radiation Hazards and Protection. (First of two lectures.)

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL, W.C.1
5 P.M. Prof. A. L. d'Abreu: The Place of Surgery in the Medical Curriculum. (Holme lecture.)

Tuesday, 13th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Psychiatry.* Dr. R. E. Hemphill: Illness of Vincent Van Gogh.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Dr. Desmond O'Neill: Gynæcological Neurosis.

Wednesday, 14th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. Honor Fell: Tissue Culture in Experimental Pathology.

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Library (Scientific Research).* Dr. F. C. Kelly: Iodine in Medicine and Pharmacy since its Discovery—1811 to 1961.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Interesting Histological Sections.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. T. Holmes Sellors: Problems in the Treatment of Fallot's Tetralogy.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Mr. Solomon Bender: Habitual Abortion.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. Selwyn Baker (Vellore): Sprue.

Thursday, 15th

UNIVERSITY OF LONDON
5.30 P.M. (King's College, Strand, W.C.2.) Prof. L. Goldberg (Stockholm): Alcohol and Addiction.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
8 P.M. Prof. P. C. C. Garnham: The Vector of *Hepatocystis* (= *Plasmodium*) *kochi*.

BRITISH ASSOCIATION OF UROLOGICAL SURGEONS
9 A.M. (Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh, 8.) Opening of 3-day meeting.

Friday, 16th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. N. W. Roberts: Osteochondritis Dissecans.